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(57) Abstract

The present invention provides methods to treat or prevent neoplasia disorders in a mammal using a combination of a cyclooxygenase-2 inhibitor, a matrix metalloproteinase inhibitor and an antineoplastic agent.

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# METHOD OF USING A CYCLOOXYGENASE-2 INHIBITOR AND AN MATRIX METALLOPROTEINASE INHIBITOR AS A COMBINATION THERAPY IN THE TREATMENT OF NEOPLASIA

5 Field of the Invention

The present invention relates to combinations and methods for treatment or prevention of neoplasia disorders in a mammal using two or more components with at least one component being an antiangiogenesis agent.

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#### Background of the Invention

A neoplasm, or tumor, is an abnormal, unregulated, and disorganized proliferation of cell growth. A neoplasm is malignant, or cancerous, if it has properties of destructive growth, invasiveness and metastasis. Invasiveness refers to the local spread of a neoplasm by infiltration or destruction of surrounding tissue, typically breaking through the basal laminas that define the boundaries of the tissues, thereby often entering the body's circulatory system. Metastasis typically refers to the dissemination of tumor cells by lymphotics or blood vessels. Metastasis also refers to the migration of tumor cells by direct extension through serous cavities, or subarachnoid or other spaces. Through the process of metastasis, tumor cell migration to other areas of the body establishes neoplasms in areas away from the site of initial appearance. Cancer is now the second leading cause of death in the United States and over 8,000,000 persons in the United States have been diagnosed with cancer. In 1995, cancer

accounted for 23.3% of all deaths in the United States.

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(See U.S. Dept. of Health and Human Services, National Center for Health Statistics, Health United States 1996-97 and Injury Chartbook 117 (1997)).

Cancer is not fully understood on the molecular 5 level. It is known that exposure of a cell to a carcinogen such as certain viruses, certain chemicals, or radiation, leads to DNA alteration that inactivates a "suppressive" gene or activates an "oncogene". Suppressive genes are growth regulatory genes, which 10 upon mutation, can no longer control cell growth. Oncogenes are initially normal genes (called prooncogenes) that by mutation or altered context of expression become transforming genes. The products of transforming genes cause inappropriate cell growth. More 15 than twenty different normal cellular genes can become oncogenes by genetic alteration. Transformed cells differ from normal cells in many ways, including cell morphology, cell-to-cell interactions, membrane content, cytoskeletal structure, protein secretion, gene 20 expression and mortality (transformed cells can grow indefinitely).

Cancer is now primarily treated with one or a combination of three types of therapies: surgery, radiation, and chemotherapy. Surgery involves the bulk removal of diseased tissue. While surgery is sometimes effective in removing tumors located at certain sites, for example, in the breast, colon, and skin, it cannot be used in the treatment of tumors located in other areas, such as the backbone, nor in the treatment of disseminated neoplastic conditions such as leukemia.

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Chemotherapy involves the disruption of cell replication or cell metabolism. It is used most often in the treatment of breast, lung, and testicular cancer.

The adverse effects of systemic chemotherapy used 5 in the treatment of neoplastic disease is most feared by patients undergoing treatment for cancer. Of these adverse effects nausea and vomiting are the most common and severe side effects. Other adverse side effects include cytopenia, infection, cachexia, mucositis in 10 patients receiving high doses of chemotherapy with bone marrow rescue or radiation therapy; alopecia (hair loss ); cutaneous complications (see M.D. Abeloff, et al: Alopecia and Cutaneous Complications. P. 755-56. In Abeloff, M.D., Armitage, J.O., Lichter, A.S., and 15 Niederhuber, J.E. (eds) Clinical Oncology. Churchill Livingston, New York, 1992, for cutaneous reactions to chemotherapy agents), such as pruritis, urticaria, and angioedema; neurological complications; pulmonary and cardiac complications in patients receiving radiation or 20 chemotherapy; and reproductive and endocrine complications.

Chemotherapy-induced side effects significantly impact the quality of life of the patient and may dramatically influence patient compliance with treatment.

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Additionally, adverse side effects associated with chemotherapeutic agents are generally the major dose-limiting toxicity (DLT) in the administration of these drugs. For example, mucositis, is one of the major dose limiting toxicity for several anticancer agents, including the antimetabolite cytotoxic agents 5-FU,

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methotrexate, and antitumor antibiotics, such as doxorubicin. Many of these chemotherapy-induced side effects if severe, may lead to hospitalization, or require treatment with analgesics for the treatment of pain.

The adverse side effects induced by chemotherapeutic agents and radiation therapy have become of major importance to the clinical management of cancer patients.

10 FR 2,771,005 describes compositions containing a cyclooxygenase-2 inhibitor and a N-methyl-d-aspartate (NMDA) antagonist used to treat cancer and other diseases. WO 99/18,960 describes a combination comprising a cyclooxygenase-2 inhibitor and an induced nitric-oxide synthase inhibitor (iNOS) that can be used 15 to treat colorectal and breast cancer. WO 99/13,799 describes the combination of a cyclooxygenase-2 inhibitor and an opioid analgesic. WO 98/41,511 describes 5-(4-sulphunyl-phenyl)-pyridazinone 20 derivatives used for treating cancer. describes (methylsulphonyl)phenyl-2-(5H)-furanone derivatives that can be used in the treatment of cancer. WO 98/16,227 describes the use of cyclooxygenase-2 inhibitors in the treatment or prevention of neoplasia. WO 97/36,497 describes a combination comprising a 25 cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor useful in treating cancer. WO 97/29,776 describes a composition comprising a cyclooxygenase-2 inhibitor in combination with a leukotriene B4 receptor 30 antagonist and an immunosuppressive drug. WO 97/29,775

describes the use of a cyclooxygenase-2 inhibitor in

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combination with a leukotriene A4 hydrolase inhibitor and an immunosuppressive drug. WO 97/29,774 describes the combination of a cyclooxygenase-2 inhibitor and protstaglandin or antiulcer agent useful in treating cancer. WO 97/11,701 describes a combination comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist useful in treating colorectal cancer. WO 96/41,645 describes a combination comprising a cyclooxygenase-2 inhibitor and a leukotriene A hydrolase inhibitor. WO 96/03,385 describes 3,4,-Di substituted pyrazole compounds given alone or in combination with NSAIDs, steroids, 5-LO inhibitors, LTB4 antagonists, or LTA4 hydrolase inhibitors that may be useful in the treatment of cancer. WO 98/47,890 describes substituted benzopyran derivatives that may be used alone or in combination with other active principles. WO 98/16,227 describes a method of using cyclooxygenase-2 inhibitors in the treatment and prevention of neoplasia.

20 U.S. Patent No. 5,854,205 describes an isolated endostatin protein that is an inhibitor of endothelial cell proliferation and angiogenesis. U.S. Patent No. 5,843,925 describes a method for inhibiting angiogenesis and endothelial cell proliferation using a 7-[substituted amino]-9-[(substituted glycyloamido]-6-demethyl-6-deoxytetracycline. U.S. Patent No. 5,863,538 describes methods and compositions for targeting tumor vasculature of solid tumors using immunological and growth factor-based reagents in combination with chemotherapy and radiation. U.S. Patent No. 5,837,682 describes the use of fragments of an endothelial cell

proliferation inhibitor, angiostatin. U.S. Patent No. 5,861,372 describes the use of an aggregate endothelial inhibitor, angiostatin, and it use in inhibiting angiogenesis. U.S. Patent No. 5,885,795 describes methods and compositions for treating diseases mediated by undesired and uncontrolled angiogenesis by administering purified angiostatin or angiostatin derivatives.

PCT/GB97/00650 describes the use of cinnoline

derivatives for use in the production of an antiangiogenic and/or vascular permeability reducing effect. PCT/US97/09610 describes administration of an anti-endogin monoclonal antibody, or fragments thereof, which is conjugated to at least one angiogenesis

inhibitor or antitumor agent for use in treating tumor and angiogenesis-associated diseases. PCT/IL96/00012 describes a fragment of the Thrombin B-chain for the treatment of cancer. PCT/US95/16855 describes compositions and methods of killing selected tumor cells using recombinant viral vectors.

Ravaud, A. et al. describes the efficacy and tolerance of interleukin-2 (IL-2), interferon alpha-2a, and fluorouracil in patients with metastatic renal cell carcinoma. J.Clin.Oncol. 16, No. 8, 2728-32, 1998.

- 25 Stadler, W.M. et al. describes the response rate and toxicity of oral 13-cis-retinoic acid added to an outpatient regimen of subcutaneous interleukin-2 and interferon alpha in patients with metastatic renal cell carcinoma. J.Clin.Oncol. 16, No. 5, 1820-25, 1998
- Rosenbeg, S.A. et al. describes treatment of patients with metastatic melanoma using chemotherapy with

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cisplatin, dacarbazine, and tamoxifen alone or in combination with interleukin-2 and interferon alpha-2b. J.Clin.Oncol. 17, No. 3, 968-75, 1999. Tourani, J-M. et al describes treatment of renal cell carcinoma using interleukin-2, and interferon alpha-2a administered in combination with fluorouracil. J.Clin.Oncol. 16, No. 7, 2505-13, 1998. Majewski, S. describes the anticancer action of retinoids, vitamin D3 and cytokines (interferons and interleukin-12) as related to the antiangiogenic and antiproliferative effects. 10 J.Invest.Dermatol. 108, No. 4, 571, 1997. Ryan, C.W. describes treatment of patients with metastatic renal cell cancer w\*ith GM-CSF, Interleukin-2, and interferonalpha plus oral cis-retinoic acid in patients with metastatic renal cell cancer. J. Invest. Med. 46, No. 7, 15 274A, 1998. Tai-Ping, D. describes potential antiangiogenic therapies. Trends Pharmacol.Sci. 16, No. 2, 57-66, 1995. Brembeck, F.H. describes the use of 13cis retinoic acid and interferon alpha to treat UICC stage III/IV pancreatic cancer. Gastroenterology 114, 20 No. 4, Pt. 2, A569, 1998. Brembeck, F.H. describes the use of 13-cis retinoic acid and interferon alpha in patients with advanced pancreatic carcinoma. Cancer 83, No. 11, 2317-23, 1998. Mackean, M.J. describes the use of roquinimex (Linomide) and alpha interferon in 25 patients with advanced malignant melanoma or renal carcinoma. Br.J.Cancer 78, No. 12, 1620-23, 1998 Jayson, G.C. describes the use of interleukin 2 and interleukin -interferon alpha in advanced renal cancer. Br.J.Cancer 78, No. 3, 366-69, 1998. Abraham, J.M. 30

describes the use of Interleukin-2, interferon alpha and

5-fluorouracil in patients with metastatic renal carcinoma. Br.J.Cancer 78, Suppl. 2, 8, 1998. Soori, G.S. describes the use of chemo-biotherapy with chlorambucil and alpha interferon in patients with nonhodgkins lymphoma. Blood 92, No. 10, Pt. 2 Suppl. 1, 240b, 1998. Enschede, S.H. describes the use of interferon alpha added to an anthracycline-based regimen in treating low grade and intermediate grade nonhodgkin's lymphoma. Blood 92, No. 10, Pt. 1 Suppl. 1, 412a, 1998. Schachter, J. describes the use of a 10 sequential multi-drug chemotherapy and biotherapy with interferon alpha, a four drug chemotherapy regimen and GM-CSF. Cancer Biother.Radiopharm. 13, No. 3, 155-64, 1998. Mross, K. describes the use of retinoic acid, interferon alpha and tamoxifen in metastatic breast 15 cancer patients. J. Cancer Res. Clin. Oncology. 124 Suppl. 1 R123, 1998. Muller, H. describes the use of suramin and tamoxifen in the treatment of advanced and metastatic pancreatic carcinoma. Eur.J.Cancer 33, Suppl. 8, S50, 1997. Rodriguez, M.R. describes the use 20 of taxol and cisplatin, and taxotere and vinorelbine in the treatment of metastatic breast cancer. Eur.J.Cancer 34, Suppl. 4, S17-S18, 1998. Formenti, C. describes concurrent paclitaxel and radiation therapy in locally advanced breast cancer patients. Eur.J.Cancer 34, 25 Suppl. 5, S39, 1998. Durando, A. describes combination chemotherapy with paclitaxel (T) and epirubicin (E) for metastatic breast cancer. Eur.J.Cancer 34, Suppl. 5, S41, 1998. Osaki, A. describes the use of a combination therapy with mitomycin-C, etoposide, doxifluridine and 30 medroxyprogesterone acetate as second-line therapy for

advanced breast cancer. Eur.J.Cancer 34, Suppl. 5, S59, 1998.

The use of TNP-470 and minocycline in combination with cyclophasphamide, CDDP, or thiotepa have been observed to substantially increase the tumor growth delay in one pre-clinical solid tumor model. (Teicher, B. A. et al., Breast Cancer Research and Treatment, 36: 227-236, 1995). Additionally, improved results were observed when the antiangiogenesis agents were used in combination with cyclophosphamide and fractionated radiation therapy. (Teicher, B. A. et al., European Journal of Cancer 32A(14): 2461-2466, 1996).

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Neri et al. examined the use of AG-3340 in combination with carboplatin and taxol for the treatment of cancer. (Neri et al., Proc Am Assoc Can Res, Vol 39, 89 meeting, 302 1998). U.S. Patent No. 5,837,696 describes the use of tetracycline compounds to inhibit cancer growth. WO 97/48,685 describes various substituted compounds that inhibit metalloproteases.

EP 48/9,577 describes peptidyl derivatives used to prevent tumor cell metastasis and invasion.

WO 98/25,949 describes the use of N5-substituted 5-amino-1,3,4-thiadiazole-2-thiols to inhibit metallopreteinase enzymes. WO 99/21,583 describes a method of inhibiting metastases in patients having cancer in which wildtype p53 is predominantly expressed using a combination of radiation therapy and a selective matrix metalloproteinase-2 inhibitor. WO 98/33,768 describes arylsulfonylamino hydroxamic acid derivatives in the treatment of cancer.

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WO 98/30,566 describes cyclic sulfone derivatives useful in the treatment of cancer.

WO 98/34,981 describes arylsulfonyl hydroxamic acid derivatives useful in the treatment of cancer.

WO 98/33,788 discloses the use of carboxylic or hyroxamic acid derivatives for treatment of tumors.

WO 97/41,844 describes a method of using combinations of angiostatic compounds for the prevention and/or treatment of neovascularization in human patients.

EP 48/9,579 describes peptidyl derivatives with selective gelatinase action that may be of use in the treatment of cancer and to control tumor metastases.

WO 98/11,908 describes the use of carboxylic or

15 hyroxamic acid derivatives and a cyclosporin in

combination therapy for treating mammals suffering from

arthritic disease.

WO 98/03,516 describes phasphinate based compounds useful in the treatment of cancer.

WO 95/23,811 describes novel carbocyclic compounds which inhibit platelet aggregation.

WO 93/24,475 describes sulphamide derivatives may be useful in the treatment of cancer to control the development of metastases.

25 WO 98/16,227 describes a method of using [Pyrozol-1-yl]benzenesulfonamides in the treatment of and prevention of neoplasia.

WO 98/22,101 describes a method of using [Pyrozol-1-yl]benzenesulfonamides as anti-angiogenic agents.

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#### Description of the Invention

A method for treating or preventing a neoplasia disorder in a mammal, including a human, 5 in need of such treatment or prevention is provided. The method comprises treating the mammal with a therapeutically effective amount of a combination comprising two or more components, the first component is a cyclooxygenase-2 inhibitor, 10 the second component is a MMP inhibitor, and the additional component or components is optionally selected from (a) an antiangiogenesis agent; (b) an antineoplastic agent; (c) an adjunctive agent; (d) an immunotherapeutic agent; (e) a device; (f) a 15 vaccine; (g) an analgesic agent; and (h) a radiotherapeutic agent; provided that the additional component(s) is other than the cycloxygenase-2 inhibitor selected as the first component and the matrix metalloproteinase 20 inhibitor selected as the second component. In one embodiment the combination comprises a

cyclooxygenase-2 inhibitor, a matrix metalloproteinase inhibitor and an antineoplastic agent.

Besides being useful for human treatment, the present invention is also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

The methods and combinations of the present invention may be used for the treatment or prevention of WO 00/37107

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neoplasia disorders including acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cycstic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma,

- basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial
- 10 hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, hemangiblastomas, hemangioendothelioma,
- hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant
- melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial,
- osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor,

squamous carcinoma, squamous cell carcinoma,

submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

The methods and combinations of the present invention provide one or more benefits. Combinations of COX-2 inhibitors and MMP inhibitors with the compounds, compositions, agents and therapies of the present invention are useful in treating and preventing

10 neoplasia disorders. Preferably, the COX-2inhibitors and MMP inhibitors or agents and the compounds, compositions, agents and therapies of the present invention are administered in combination at a low dose, that is, at a dose lower than has been conventionally used in clinical situations.

A benefit of lowering the dose of the compounds, compositions, agents and therapies of the present invention administered to a mammal includes a decrease in the incidence of adverse effects associated with higher dosages. For example, by the lowering the dosage of a chemotherapeutic agent such as methotrexate, a reduction in the frequency and the severity of nausea and vomiting will result when compared to that observed at higher dosages. Similar benefits are contemplated for the compounds, compositions, agents and therapies in combination with the COX-2inhibitors and MMP inhibitors of the present invention.

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By lowering the incidence of adverse effects, an improvement in the quality of life of a patient

30 undergoing treatment for cancer is contemplated.

Further benefits of lowering the incidence of adverse

effects include an improvement in patient compliance, a reduction in the number of hospitalizations needed for the treatment of adverse effects, and a reduction in the administration of analgesic agents needed to treat pain associated with the adverse effects.

Alternatively, the methods and combination of the present invention can also maximize the therapeutic effect at higher doses.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

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When used as a therapeutic the compounds described herein are preferably administered with a

15 physiologically acceptable carrier. A physiologically acceptable carrier is a formulation to which the compound can be added to dissolve it or otherwise facilitate its administration. Examples of physiologically acceptable carriers include, but are not limited to, water, saline, physiologically buffered saline. Additional examples are provided below.

The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product.

25 Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences.

Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (Nmethylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, 10 malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the 15 like.

A compound of the present invention can be formulated as a pharmaceutical composition. composition can then be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing 20 conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used 25 herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania; 30 1975. Another example of includes Liberman, H.A. and

Lachman, L., Eds., <u>Pharmaceutical Dosage Forms</u>, Marcel Decker, New York, N.Y., 1980.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable 5 dispersing or wetting agents and suspending agents. sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable dilutent or solvent, for example, as a solution in 1,3-butanediol. Among the 10 acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be 15 employed including synthetic mono- or diglycerides. addition, fatty acids such as oleic acid find use in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, polyethylene glycols can be used. Mixtures of solvents 20 and wetting agents such as those discussed above are also useful.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are sold at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

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Solid dosage forms for oral administration can include capsules, tablets, pills, powders, and granules.

In such solid dosage forms, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, a contemplated aromatic sulfone hydroximate inhibitor compound can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, 10 polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlledrelease formulation as can be provided in a dispersion 15 of active compound in hydroxypropylmethyl cellulose. the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with 20 enteric coatings.

For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. A contemplated aromatic sulfone hydroximate inhibitor compound can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or

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various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

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Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.

The present invention further includes kits comprising a cyclooxygenase-2 inhibitor, a MMP inhibitor, and optionally an antineoplastic agent.

The term "treatment" refers to any process, action, application, therapy, or the like, wherein a mammal, including a human being, is subject to medical aid with the object of improving the mammal's condition, directly or indirectly.

The term "inhibition," in the context of neoplasia, tumor growth or tumor cell growth, may be assessed by delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, among others. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention.

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The term "prevention" includes either preventing the onset of clinically evident neoplasia altogether or preventing the onset of a preclinically evident stage of neoplasia in individuals at risk. Also intended to be encompassed by this definition is the prevention of initiation for malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment of those at risk of developing the neoplasia.

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The term "angiogenesis" refers to the process by which tumor cells trigger abnormal blood vessel growth to create their own blood supply, and is a major target of cancer research. Angiogenesis is believed to be the mechanism via which tumors get needed nutrients to grow and metastasize to other locations in the body.

Antiangiogenic agents interfere with these processes and destroy or control tumors.

Angiogenesis is an attractive therapeutic target because it is a multi-step process that occurs in a specific sequence, thus providing several possible targets for drug action. Examples of agents that interfere with several of these steps include thrombospondin-1, angiostatin, endostatin, interferon alpha and compounds such as matrix metalloproteinase (MMP) inhibitors that block the actions of enzymes that clear and create paths for newly forming blood vessels to follow; compounds, such as  $\alpha\nu\beta$ 3 inhibitors, that interfere with molecules that blood vessel cells use to bridge between a parent blood vessel and a tumor; agents, such as specific COX-2 inhibitors, that prevent the growth of cells that form new blood vessels; and

protein-based compounds that simultaneously interfere with several of these targets.

Antiangiogenic therapy may offer several advantages over conventional chemotherapy for the treatment of cancer.

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Antiangiogenic agents have low toxicity in preclinical trials and development of drug resistance has not been observed (Folkman, J., Seminars in Medicine of the Beth Israel Hospital, Boston 333(26): 1757-1763, 1995). As angiogenesis is a complex process, made up of many steps including invasion, proliferation and migration of endothelial cells, it can be anticipated that combination therapies will be most effective. Kumar and Armstrong describe anti-angiogenesis therapy used as an adjunct to chemotherapy, radiation therapy, or surgery. (Kumar, CC, and Armstrong, L., Tumor-induced angiogenesis: a novel target for drug therapy?, Emerging Drugs (1997), 2, 175-190).

The phrase "therapeutically-effective" is intended to qualify the amount of each agent that will achieve the goal of improvement in neoplastic disease severity and the frequency of neoplastic disease over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

A "therapeutic effect" or "therapeutic effective amount" is intended to qualify the amount of an anticancer agent required to relieve to some extent one or more of the symptoms of a neoplasia disorder, including, but is not limited to: 1) reduction in the number of cancer cells; 2) reduction in tumor size; 3) inhibition (i.e., slowing to some extent, preferably

stopping) of cancer cell infiltration into peripheral organs; 3) inhibition (i.e., slowing to some extent, preferably stopping) of tumor metastasis; 4) inhibition, to some extent, of tumor growth; 5) relieving or reducing to some extent one or more of the symptoms associated with the disorder; and/or 6) relieving or reducing the side effects associated with the administration of anticancer agents.

The phrase "combination therapy" (or "co-therapy") embraces the administration of a cyclooxygenase-2 10 inhibitor, a metalloproteinase inhibitor, and optionally an antineoplastic agent as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited 15 to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending 20 upon the combination selected). "Combination therapy" generally is not intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations 25 of the present invention. "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, 30 or at least two of the therapeutic agents, in a

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substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, 10 intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other two therapeutic agents of the 15 combination may be administered orally. Alternatively, for example, all three therapeutic agents may be administered orally or all three therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not 20 narrowly critical. "Combination therapy" also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients (such as, but not 25 limited to, a second and different antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). Where the combination therapy further comprises radiation treatment, the radiation treatment may be conducted at any suitable 30 time so long as a beneficial effect from the co-action

of the combination of the therapeutic agents and

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radiation treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the radiation treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

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The phrases "low dose" or "low dose amount", in characterizing a therapeutically effective amount of the antiangiogenesis agent and the antineoplastic agent or therapy in the combination therapy, defines a quantity of such agent, or a range of quantity of such agent, that is capable of improving the neoplastic disease severity while reducing or avoiding one or more antineoplastic-agent-induced side effects, such as myelosupression, cardiac toxicity, alopecia, nausea or vomiting.

The phrase "adjunctive therapy" encompasses treatment of a subject with agents that reduce or avoid side effects associated with the combination therapy of the present invention, including, but not limited to, those agents, for example, that reduce the toxic effect of anticancer drugs, e.g., bone resorption inhibitors, cardioprotective agents; prevent or reduce the incidence of nausea and vomiting associated with chemotherapy, radiotherapy or operation; or reduce the incidence of infection associated with the administration of myelosuppressive anticancer drugs.

The phrase an "immunotherapeutic agent" refers to agents used to transfer the immunity of an immune donor, e.g., another person or an animal, to a host by inoculation. The term embraces the use of serum or gamma gobulin containing performed antibodies produced

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by another individual or an animal; nonspecific systemic stimulation; adjuvants; active specific immunotherapy; and adoptive immunotherapy. Adoptive immunotherapy refers to the treatment of a disease by therapy or agents that include host inoculation of sensitized lymphocytes, transfer factor, immune RNA, or antibodies in serum or gamma globulin.

The phrase a "device" refers to any appliance, usually mechanical or electrical, designed to perform a particular function.

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The phrase a "vaccine" includes agents that induce the patient's immune system to mount an immune response against the tumor by attacking cells that express tumor associated antigens (TAAs).

The phrase "multi-functional proteins" encompass a variety of pro-angiogenic factors that include basic and acid fibroblast growth factors (bFGF and aFGF) and vascular permeability factor/vascular endothelial growth factor (VPF/VEGF) ( Bikfalvi, A. et al., Endocrine

- Reviews 18: 26-45, 1997). Several endogenous antiangiogenic factors have also been characterized as multi-functional proteins and include angiostatin (O'Reilly et al., Cell (Cambridge, Mass) 79(2): 315-328, 1994), endostatin (O'Reilly et al, Cell (Cambridge,
- 25 Mass) 88(2): 277-285, 1997), interferon .alpha.
   (Ezekowitz et al, N. Engl. J. Med., May 28, 326(22)
   1456-1463, 1992), thrombospondin (Good et al, Proc Natl
   Acad Sci USA 87(17): 6624-6628, 1990; Tolsma et al, J
   Cell Biol 122(2): 497-511, 1993), and platelet factor 4
- 30 (PF4) (Maione et al, Science 247: (4938): 77-79, 1990).

The phrase an "analgesic agent" refers to an agent that relieves pain without producing anesthesia or loss of consciousness generally by altering the perception of nociceptive stimuli.

The phrase a "radiotherapeutic agent" refers to the use of electromagnetic or particulate radiation in the treatment of neoplasia.

The term "pBATT" embraces or "Protein-Based Anti-Tumor Therapies," refers to protein-based therapeutics for solid tumors. The PBATTs are including proteins that have demonstrated efficacy against tumors in animal models or in humans. The protein is then modified to increase its efficacy and toxicity profile by enhancing its bioavailability and targeting.

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15 "Angiostatin" is a 38 kD protein comprising the first three or four kringle domains of plasminogen and was first described in 1994 (O'Reilly, M. S. et al., Cell (Cambridge, Mass.) 79(2): 315-328, 1994). Mice bearing primary (Lewis lung carcinoma-low metastatic) 20 tumors did not respond to angiogenic stimuli such as bFGF in a corneal micropocket assay and the growth of metastatic tumors in these mice was suppressed until the primary tumor was excised. The factor responsible for the inhibition of angiogenesis and tumor growth was designated mouse angiostatin. Angiostatin was also 25 shown to inhibit the growth of endothelial cells in vitro.

Human angiostatin can be prepared by digestion of plasminogen by porcine elastase (O'Reilly, et al., Cell 79(2): 315-328, 1994) or with human metalloelastase (Dong et al., Cell 88, 801-810, 1997). The angiostatin

produced via porcine elastase digestion inhibited the growth of metastases and primary tumors in mice.

O'Reilly et al (Cell 79(2): 315-328, 1994) demonstrated that human angiostatin inhibited metastasis of Lewis lung carcinoma in SCID mice. The same group (O'Reilly, M. S. et al., Nat. Med. (N. Y.) 2(6): 689-692, 1996) subsequently showed that human angiostatin inhibited the growth of the human tumors PC3 prostate carcinoma, clone A colon carcinoma, and MDA-MB breast carcinoma in SCID mice. Human angiostatin also inhibited the growth of the mouse tumors Lewis lung carcinoma, T241 fibrosarcoma and M5076 reticulum cell carcinoma in C57Bl mice.

Because these enzymatically-prepared angiostatins are not well characterized biochemically, the precise composition of the molecules is not known.

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Angiostatins of known composition can be prepared by means of recombinant DNA technology and expression in heterologous cell systems. Recombinant human angiostatin comprising Kringle domains one through four (K1-4) has been produced in the yeast *Pichia pastoris* (Sim et al., *Cancer Res* 57: 1329-1334, 1997). The recombinant human protein inhibited growth of endothelial cells in vitro and inhibited metastasis of Lewis lung carcinoma in C57Bl mice. Recombinant murine angiostatin (K1-4) has been produced in insect cells (Wu et al., *Biochem Biophys Res Comm* 236: 651-654, 1997). The recombinant mouse protein inhibited endothelial cell growth in vitro and growth of primary Lewis lung carcinoma *in vivo*. These experiments demonstrated that the first four kringle domains are sufficient for

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angiostatin activity but did not determine which kringle domains are necessary.

Cao et al. (J. Biol. Chem. 271: 29461-29467, 1996), produced fragments of human plasminogen by proteolysis and by expression of recombinant proteins in E. coli. These authors showed that kringle one and to a lesser extent kringle four of plasminogen were responsible for the inhibition of endothelial cell growth in vitro. Specifically, kringles 1-4 and 1-3 inhibited at similar concentrations, while K1 alone inhibited endothelial 10 cell growth at four-fold higher concentrations. Kringles two and three inhibited to a lesser extent. More recently Cao et al. (J Biol Chem 272: 22924-22928, 1997), showed that recombinant mouse or human kringle five inhibited endothelial cell growth at lower 15 concentrations than angiostatin (K1-4). These experiments demonstrated in vitro angiostatin-like activity but did not address in vivo action against tumors and their metastases.

World patent applications WO 95/29242 A1, WO
96/41194 A1, and WO 96/35774 A2 describe the expression,
purification, and characterization of angiostatin. WO
95/29242 A1 951102 discloses purification of a protein
from blood and urine by HPLC that inhibits proliferation
of endothelial cells. The protein has a molecular
weight between 38 kilodaltons and 45 kilodaltons and an
amino acid sequence substantially similar to that of a
murine plasminogen fragment beginning at amino acid
number 79 of a murine plasminogen molecule. WO 96/41194
A1 961219, discloses compounds and methods for the
diagnosis and monitoring of angiogenesis-dependent

diseases. WO 96/35774 A2 961114 discloses the structure of protein fragments, generally corresponding to kringle structures occurring within angiostatin. It also discloses aggregate forms of angiostatin, which have endothelial cell inhibiting activity, and provides a means for inhibiting angiogenesis of tumors and for treating angiogenic-mediated diseases.

"Endostatin" is a 20-kDa (184 amino acid) carboxy fragment of collagen XVIII, is an angiogenesis inhibitor produced by a hemangioendothelioma (O'Reilly, M. S. et al., Cell (Cambridge, Mass.) 88(2): 277-285, 1997); and WO 97/15666). Endostatin specifically inhibits endothelial proliferation and inhibits angiogenesis and tumor growth. Primary tumors treated with non-refolded suspensions of E. coli-derived endostatin regressed to dormant microscopic lesions. Toxicity was not observed and immunohistochemical studies revealed a blockage of angiogenesis accompanied by high proliferation balanced by apoptosis in tumor cells.

- "Interferon .alpha." (IFN.alpha.) is a family of highly homologous, species-specific proteins that possess complex antiviral, antineoplastic and immunomodulating activities (Extensively reviewed in the monograph "Antineoplastic agents, interferon alfa",
- 25 American Society of Hospital Pharmacists, Inc., 1996).
  Interferon .alpha. also has anti-proliferative, and antiangiogenic properties, and has specific effects on cellular differentiation (Sreevalsan, in "Biologic Therapy of Cancer", pp. 347-364, (eds. V.T. DeVita Jr.,
- 30 S. Hellman, and S.A. Rosenberg), J.B. Lippincott Co, Philadelphia, PA, 1995).

Interferon .alpha. is effective against a variety of cancers including hairy cell leukemia, chronic myelogenous leukemia, malignant melanoma, and Kaposi's sarcoma. The precise mechanism by which IFN.alpha.

5 exerts its anti-tumor activity is not entirely clear, and may differ based on the tumor type or stage of disease. The anti-proliferative properties of IFN.alpha., which may result from the modulation of the expression of oncogenes and/or proto-oncogenes, have been demonstrated on both tumor cell lines and human tumors growing in nude mice (Gutterman, J. U., Proc. Natl. Acad. Sci., USA 91: 1198-1205, 1994).

Interferon is also considered an anti-angiogenic factor, as demonstrated through the successful treatment of hemangiomas in infants (Ezekowitz et al, N. Engl. J. Med., May 28, 326(22) 1456-1463, 1992) and the effectiveness of IFN.alpha. against Kaposi's sarcoma (Krown, Semin Oncol 14(2 Suppl 3): 27-33, 1987). The mechanism underlying these anti-angiogenic effects is not clear, and may be the result of IFN.alpha. action on the tumor (decreasing the secretion of pro-angiogenic factors) or on the neo-vasculature. IFN receptors have been identified on a variety of cell types (Navarro et al., Modern Pathology 9(2): 150-156, 1996).

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United States Patent 4,530,901, by Weissmann, describes the cloning and expression of IFN-.alpha.-type molecules in transformed host strains. United States Patent 4,503,035, Pestka, describes an improved processes for purifying 10 species of human leukocyte interferon using preparative high performance liquid chromatography. United States Patent 5,231,176,

Goeddel, describes the cloning of a novel distinct family of human leukocyte interferons containing in their mature form greater than 166 and no more than 172 amino acids.

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United States Patent 5,541,293, by Stabinsky, describes the synthesis, cloning, and expression of consensus human interferons. These are non-naturally occurring analogues of human (leukocyte) interferonalpha. assembled from synthetic oligonucleotides. The sequence of the consensus interferon was determined by comparing the sequences of 13 members of the IFN-.alpha. family of interferons and selecting the preferred amino acid at each position. These variants differ from naturally occurring forms in terms of the identity and/or location of one or more amino acids, and one or more biological and pharmacological properties (e.g., antibody reactivity, potency, or duration effect) but retain other such properties.

"Thrombospondin-1" (TSP-1) is a trimer containing three copies of a 180 kDa polypeptide. TSP-1 is 20 produced by many cell types including platelets, fibroblasts, and endothelial cells (see Frazier, Curr Opin Cell Biol 3(5): 792-799, 1991) and the cDNA encoding the subunit has been cloned (Hennessy, et al., 1989, J Cell Biol 108(2): 729-736; Lawler and Hynes, J 25 Cell Biol 103(5): 1635-1648, 1986). Native TSP-1 has been shown to block endothelial cell migration in vitro and neovascularization in vivo (Good et al, Proc Natl Acad Sci USA 87(17): 6624-6628, 1990). Expression of TSP-1 in tumor cells also suppresses tumorigenesis and 30 tumor-induced angiogenesis (Sheibani and Frazier, Proc

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Natl Acad Sci USA 92(15) 6788-6792, 1995; Weinstat-Saslow et al., Cancer Res 54(24):6504-6511, 1994). The antiangiogenic activity of TSP-1 has been shown to reside in two distinct domains of this protein (Tolsma et al, J Cell Biol 122(2): 497-511, 1993). One of these domains consists of residues 303 to 309 of native TSP-1 and the other consists of residues 481 to 499 of TSP-1. Another important domain consists of the sequence CSVTCG which appears to mediate the binding of TSP-1 to some tumor cell types (Tuszynski and Nicosia, Bioessays 10 18(1): 71-76, 1996). These results suggest that CSVTCG, or related sequences, can be used to target other moieties to tumor cells. Taken together, the available data indicate that TSP-1 plays a role in the growth and 15 vascularization of tumors. Subfragments of TSP-1, then, may be useful as antiangiogenic components of chimeras and/or in targeting other proteins to specific tumor cells. Subfragments may be generated by standard procedures (such as proteolytic fragmentation, or by DNA 20 amplification, cloning, expression, and purification of specific TSP-1 domains or subdomains) and tested for antiangiogenic or anti-tumor activities by methods known in the art (Tolsma et al, *J Cell Biol* 122(2): 497-511, 1993; Tuszynski and Nicosia, Bioessays 18(1): 71-76, 25 1996).

The phrase "integrin antagonist" includes agents that impair endothelial cell adhesion via the various integrins. Integrin antagonists induce improperly proliferating endothelial cells to die, by interfering with molecules that blood vessel cells use to bridge between a parent blood vessel and a tumor.

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Adhesion forces are critical for many normal physiological functions. Disruptions in these forces, through alterations in cell adhesion factors, are implicated in a variety of disorders, including cancer, stroke, osteoporosis, restenosis, and rheumatoid arthritis (A. F. Horwitz, *Scientific American*, 276:(5): 68-75, 1997).

Integrins are a large family of cell surface glycoproteins which mediate cell adhesion and play central roles in many adhesion phenomena. Integrins are heterodimers composed of noncovalently linked a and b polypeptide subunits. Currently eleven different a subunits have been identified and six different  $\beta$  subunits have been identified. The various a subunits can combine with various b subunits to form distinct integrins.

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One integrin known as a,b, (or the vitronectin receptor) is normally associated with endothelial cells and smooth muscle cells. A,b, integrins can promote the formation of blood vessels (angiogenesis) in tumors. These vessels nourish the tumors and provide access routes into the bloodstream for metastatic cells.

The a,b, integrin is also known to play a role in various other disease states or conditions including tumor metastasis, solid tumor growth (neoplasia), osteoporosis, Paget's disease, humoral hypercalcemia of malignancy, angiogenesis, including tumor angiogenesis, retinopathy, arthritis, including rheumatoid arthritis, periodontal disease, psoriasis, and smooth muscle cell migration (e.g. restenosis).

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Tumor cell invasion occurs by a three step process:

1) tumor cell attachment to extracellular matrix; 2)

proteolytic dissolution of the matrix; and 3) movement

of the cells through the dissolved barrier. This

process can occur repeatedly and can result in

metastases at sites distant from the original tumor.

The a,b, integrin and a variety of other avcontaining integrins bind to a number of Arg-Gly-Asp (RGD) containing matrix macromolecules. Compounds containing the RGD sequence mimic extracellular matrix 10 ligands and bind to cell surface receptors. Fibronectin and vitronectin are among the major binding partners of a,b, integrin. Other proteins and peptides also bind the a,b, ligand. These include the disintegrins (M. Pfaff et al., Cell Adhes. Commun. 2(6): 491-501, 1994), peptides 15 derived from phage display libraries (Healy, J.M. et al., Protein Pept. Lett. 3(1): 23-30, 1996; Hart, S.L. et al., J. Biol. Chem. 269(17): 12468-12474, 1994) and small cyclic RGD peptides (M. Pfaff et al., J. Biol. Chem., 269(32): 20233-20238, 1994). The monoclonal 20 antibody LM609 is also an a.b. integrin antagonist (D.A. Cheresh et al., J. Biol. Chem., 262(36): 17703-17711, 1987).

A,b, inhibitors are being developed as potential

25 anti-cancer agents. Compounds that impair endothelial

cell adhesion via the a,b, integrin induce improperly

proliferating endothelial cells to die.

The a<sub>v</sub>b<sub>3</sub> integrin has been shown to play a role in melanoma cell invasion (Seftor et al., *Proc. Natl. Acad. Sci. USA*, 89: 1557-1561, 1992). The a<sub>v</sub>b<sub>3</sub> integrin expressed on human melanoma cells has also been shown to

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promote a survival signal, protecting the cells from apoptosis (Montgomery et al., *Proc. Natl. Acad. Sci. USA*, **91**: 8856-8860, 1994).

Mediation of the tumor cell metastatic pathway by

interference with the a,b, integrin cell adhesion
receptor to impede tumor metastasis would be beneficial.

Antagonists of a,b, have been shown to provide a
therapeutic approach for the treatment of neoplasia
(inhibition of solid tumor growth) because systemic

administration of a,b, antagonists causes dramatic
regression of various histologically distinct human
tumors (Brooks et al., Cell, 79: 1157-1164, 1994).

The adhesion receptor identified as integrin a,b, is a marker of angiogenic blood vessels in chick and man. 15 This receptor plays a critical role in angiogenesis or neovascularization. Angiogenesis is characterized by the invasion, migration and proliferation of smooth muscle and endothelial cells by new blood vessels. Antagonists of a,b, inhibit this process by selectively 20 promoting apoptosis of cells in the neovasculature. growth of new blood vessels, also contributes to pathological conditions such as diabetic retinopathy (Adonis et al., Amer. J. Ophthal., 118: 445-450, 1994) and rheumatoid arthritis (Peacock et al., J. Exp. Med., 175:, 1135-1138, 1992). Therefore, a,b, antagonists can 25 be useful therapeutic targets for treating such conditions associated with neovascularization (Brooks et al., Science, 264: 569-571, 1994).

The a,b, cell surface receptor is also the major 30 integrin on osteoclasts responsible for the attachment to the matrix of bone. Osteoclasts cause bone resorption and when such bone resorbing activity exceeds bone forming activity, osteoporosis (a loss of bone) results, which leads to an increased number of bone fractures, incapacitation and increased mortality.

Antagonists of a,b, have been shown to be potent inhibitors of osteoclastic activity both in vitro (Sato et al., J. Cell. Biol., 111: 1713-1723, 1990) and in vivo (Fisher et al., Endocrinology, 132: 1411-1413, 1993). Antagonism of a,b, leads to decreased bone

10 resorption and therefore assists in restoring a normal balance of bone forming and resorbing activity. Thus it would be beneficial to provide antagonists of osteoclast a,b, which are effective inhibitors of bone resorption and therefore are useful in the treatment or prevention of osteoporosis.

PCT Int. Appl. WO 97/08145 by Sikorski et al., discloses meta-guanidine, urea, thiourea or azacyclic amino benzoic acid derivatives as highly specific a,b, integrin antagonists.

PCT Int. Appl. WO 96/00574 A1 960111 by Cousins, R.D. et. al., describe preparation of 3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine and -2-benzazepine derivatives and analogs as vitronectin receptor antagonists.

PCT Int. Appl. WO 97/23480 A1 970703 by Jadhav,
P.K. et. al. describe annelated pyrazoles as novel
integrin receptor antagonists. Novel heterocycles
including 3-[1-[3-(imidazolin-2-ylamino)propyl]indazol5-ylcarbonylamino]-2-(benzyl oxycarbonylamino)propionic
acid, which are useful as antagonists of the avb3
integrin and related cell surface adhesive protein

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receptors.

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PCT Int. Appl. WO 97/26250 A1 970724 by Hartman, G.D. et al., describe the preparation of arginine dipeptide mimics as integrin receptor antagonists.

- Selected compounds were shown to bind to human integrin a<sub>v</sub>b<sub>3</sub> with EIB <1000 nM and claimed as compounds, useful for inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets.
- 10 PCT Int. Appl. WO 97/23451 by Diefenbach, B. et. al. describe a series of tyrosine-derivatives used as alpha v-integrin inhibitors for treating tumors, osteoporosis, osteolytic disorder and for suppressing angiogenesis.
- PCT Int. Appl. WO 96/16983 Al 960606. by Vuori, K. and Ruoslahti, E. describe cooperative combinations of a,b, integrin ligand and second ligand contained within a matrix, and use in wound healing and tissue regeneration. The compounds contain a ligand for the a,b, integrin and a ligand for the insulin receptor, the PDGF receptor, the IL-4 receptor, or the IGF receptor, combined in a biodegradable polymeric (e.g. hyaluronic acid) matrix.

PCT Int. Appl. WO 97/10507 A1 970320 by Ruoslahti,
25 E; and Pasqualini, R. describe peptides that home to a
selected organ or tissue in vivo, and methods of
identifying them. A brain-homing peptide, nine amino
acid residues long, for example, directs red blood cells
to the brain. Also described is use of in vivo panning
30 to identify peptides homing to a breast tumor or a
melanoma.

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PCT Int. Appl. WO 96/01653 A1 960125 by Thorpe, Philip E.; Edgington, Thomas S. describes bifunctional ligands for specific tumor inhibition by blood coagulation in tumor vasculature. The disclosed bispecific binding ligands bind through a first binding region to a disease-related target cell, e.g. a tumor cell or tumor vasculature; the second region has coagulation-promoting activity or is a binding region for a coagulation factor. The disclosed bispecific 10 binding ligand may be a bispecific (monoclonal) antibody, or the two ligands may be connected by a (selectively cleavable) covalent bond, a chemical linking agent, an avidin-biotin linkage, and the like. The target of the first binding region can be a 15 cytokine-inducible component, and the cytokine can be released in response to a leukocyte-activating antibody; this may be a bispecific antibody which crosslinks activated leukocytes with tumor cells.

The phrase "matrix metalloproteinase inhibitor" or 20 "MMP inhibitor" includes agents that specifically inhibit a class of enzymes, the zinc metalloproteinases (metalloproteases). The zinc metalloproteinases are involved in the degradation of connective tissue or connective tissue components. These enzymes are 25 released from resident tissue cells and/or invading inflammatory or tumor cells. Blocking the action of zinc metalloproteinases interferes with the creation of paths for newly forming blood vessels to follow. Examples of MMP inhibitors are described in Golub, LM, 30 Inhibition of Matrix Metalloproteinases: Therapeutic Applications (Annals of the New York Academy of Science, WO 00/37107

Vol 878). Robert A. Greenwald and Stanley Zucker (Eds.), June 1999), and is hereby incorporated by reference. Connective tissue, extracellular matrix constituents and basement membranes are required components of all These components are the biological materials mammals. that provide rigidity, differentiation, attachments and, in some cases, elasticity to biological systems including human beings and other mammals. Connective tissues components include, for example, collagen, 10 elastin, proteoglycans, fibronectin and laminin. These biochemicals makeup, or are components of structures, such as skin, bone, teeth, tendon, cartilage, basement membrane, blood vessels, cornea and vitreous humor. Under normal conditions, connective tissue turnover 15 and/or repair processes are controlled and in equilibrium. The loss of this balance for whatever reason leads to a number of disease states. Inhibition of the enzymes responsible loss of equilibrium provides a control mechanism for this tissue decomposition and, 20 therefore, a treatment for these diseases.

Degradation of connective tissue or connective tissue components is carried out by the action of proteinase enzymes released from resident tissue cells and/or invading inflammatory or tumor cells. A major

class of enzymes involved in this function are the zinc metalloproteinases (metalloproteases).

The metalloprotease enzymes are divided into classes with some members having several different names in common use. Examples are: collagenase I (MMP-1, fibroblast collagenase; EC 3.4.24.3); collagenase II (MMP-8, neutrophil collagenase; EC 3.4.24.34), collagenase III (MMP-13), stromelysin 1 (MMP-3; EC 3.4.24.17), stromelysin 2 (MMP-10; EC 3.4.24.22), 10 proteoglycanase, matrilysin (MMP-7), gelatinase A (MMP-2, 72kDa gelatinase, basement membrane collagenase; EC 3.4.24.24), gelatinase B (MMP-9, 92kDa gelatinase; EC 3.4.24.35), stromelysin 3 (MMP-11), metalloelastase (MMP-12, HME, human macrophage elastase) and membrane 15 MMP (MMP-14). MMP is an abbreviation or acronym representing the term Matrix Metalloprotease with the attached numerals providing differentiation between specific members of the MMP group.

The uncontrolled breakdown of connective tissue by

20 metalloproteases is a feature of many pathological
conditions. Examples include rheumatoid arthritis,
osteoarthritis, septic arthritis; corneal, epidermal or
gastric ulceration; tumor metastasis, invasion or
angiogenesis; periodontal disease; proteinuria;

25 Alzheimer's Disease; coronary thrombosis and bone
disease. Defective injury repair processes also occur.
This can produce improper wound healing leading to weak
repairs, adhesions and scarring. These latter defects
can lead to disfigurement and/or permanent disabilities

30 as with post-surgical adhesions.

Matrix metalloproteases are also involved in the biosynthesis of tumor necrosis factor (TNF) and inhibition of the production or action of TNF and related compounds is an important clinical disease treatment mechanism. TNF- $\alpha$ , for example, is a cytokine that at present is thought to be produced initially as a 28 kD cell-associated molecule. It is released as an active, 17 kD form that can mediate a large integer of deleterious effects in vitro and in vivo. For example, TNF can cause and/or contribute to the effects of 10 inflammation, rheumatoid arthritis, autoimmune disease, multiple sclerosis, graft rejection, fibrotic disease, cancer, infectious diseases, malaria, mycobacterial infection, meningitis, fever, psoriasis, cardiovascular/pulmonary effects such as post-ischemic 15 reperfusion injury, congestive heart failure, hemorrhage, coagulation, hyperoxic alveolar injury, radiation damage and acute phase responses like those seen with infections and sepsis and during shock such as septic shock and hemodynamic shock. Chronic release of 20 active TNF can cause cachexia and anorexia. TNF can be lethal.

TNF-α convertase is a metalloproteinase involved in the formation of active TNF-α. Inhibition of TNF-α

25 convertase inhibits production of active TNF-α.

Compounds that inhibit both MMPs activity have been disclosed in, for example PCT Publication WO 94/24140.

Other compounds that inhibit both MMPs activity have also been disclosed in WO 94/02466. Still other

compounds that inhibit both MMPs activity have been disclosed in WO 97/20824.

There remains a need for effective MMP and TNF- $\alpha$  convertase inhibiting agents. Compounds that inhibit MMPs such as collagenase, stromelysin and gelatinase have been shown to inhibit the release of TNF (Gearing et al. *Nature* 376, 555-557 (1994)). McGeehan et al., *Nature* 376, 558-561 (1994) also reports such findings.

MMPs are involved in other biochemical processes in mammals as well. Included is the control of ovulation, post-partum uterine involution, possibly implantation, cleavage of APP ( $\beta$ -Amyloid Precursor Protein) to the 10 amyloid plaque and inactivation of  $\alpha_1\mbox{-protease}$  inhibitor  $(\alpha, -PI)$ . Inhibition of these metalloproteases permits the control of fertility and the treatment or prevention of Alzheimers Disease. In addition, increasing and 15 maintaining the levels of an endogenous or administered serine protease inhibitor drug or biochemical such as  $\alpha$  $_1$ -PI supports the treatment and prevention of diseases such as emphysema, pulmonary diseases, inflammatory diseases and diseases of aging such as loss of skin or 20 organ stretch and resiliency.

Inhibition of selected MMPs can also be desirable in other instances. Treatment of cancer and/or inhibition of metastasis and/or inhibition of angiogenesis are examples of approaches to the treatment of diseases wherein the selective inhibition of stromelysin (MMP-3), gelatinase (MMP-2), or collagenase III (MMP-13) are the relatively most important enzyme or enzymes to inhibit especially when compared with collagenase I (MMP-1). A drug that does not inhibit collagenase I can have a superior therapeutic profile.

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Inhibitors of metalloproteases are known. Examples include natural biochemicals such as tissue inhibitor of metalloproteinase (TIMP),  $\alpha_2$ -macroglobulin and their analogs or derivatives. These are high molecular weight protein molecules that form inactive complexes with metalloproteases. An integer of smaller peptide-like compounds that inhibit metalloproteases have been described. Mercaptoamide peptidyl derivatives have shown ACE inhibition in vitro and in vivo. Angiotensin converting enzyme (ACE) aids in the production of angiotensin II, a potent pressor substance in mammals and inhibition of this enzyme leads to the lowering of blood pressure.

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Thiol group-containing amide or peptidyl amide-15 based metalloprotease (MMP) inhibitors are known as is shown in, for example, WO 95/12389. Thiol groupcontaining amide or peptidyl amide-based metalloprotease (MMP) inhibitors are also shown in WO 96/11209. Still further Thiol group-containing amide or peptidyl amide-20 based metalloprotease (MMP) inhibitors are shown in U.S. Patent No. 4,595,700. Hydroxamate group-containing MMP inhibitors are disclosed in a number of published patent applications that disclose carbon back-boned compounds, such as in WO 95/29892. Other published patents include WO 97/24117. Additionally, EP 0 780 386 further 25 discloses hydroxamate group-containing MMP inhibitors. WO 90/05719 disclose hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones. WO 93/20047 also discloses hydroxamates that have a peptidyl back-30 bones or peptidomimetic back-bones. Additionally, WO 95/09841 discloses disclose hydroxamates that have

peptidyl back-bones or peptidomimetic back-bones. And WO 96/06074 further discloses hydroxamates that have peptidyl back-bones or peptidomimetic back-bones. Schwartz et al., Progr. Med. Chem., 29:271-334(1992)

5 also discloses disclose hydroxamates that have peptidyl back-bones or peptidomimetic back-bones. Furthermore, Rasmussen et al., Pharmacol. Ther., 75(1): 69-75 (1997) discloses hydroxamates that have peptidyl back-bones or peptidomimetic back-bones. Also, Denis et al., Invest.

10 New Drugs, 15(3): 175-185 (1997) discloses hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones as well.

One possible problem associated with known MMP inhibitors is that such compounds often exhibit the same or similar inhibitory effects against each of the MMP enzymes. For example, the peptidomimetic hydroxamate known as batimastat is reported to exhibit IC50 values of about 1 to about 20 nanomolar (nM) against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat, another peptidomimetic hydroxamate was reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum very similar to batimastat, except that marimastat exhibited an IC50 value against MMP-3 of 230 nM. Rasmussen et al., Pharmacol. Ther., 75(1): 69-75 (1997).

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Meta analysis of data from Phase I/II studies using marimastat in patients with advanced, rapidly progressive, treatment-refractory solid tumor cancers (colorectal, pancreatic, ovarian, prostate), indicated a dose-related reduction in the rise of cancer-specific antigens used as surrogate markers for biological

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activity. The most common drug-related toxicity of marimastat in those clinical trials was musculoskeletal pain and stiffness, often commencing in the small joints in the hands, spreading to the arms and shoulder. A short dosing holiday of 1-3 weeks followed by dosage reduction permits treatment to continue. Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997). It is thought that the lack of specificity of inhibitory effect among the MMPs may be the cause of that effect.

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In view of the importance of hydroxamate MMP inhibitor compounds in the treatment of several diseases and the lack of enzyme specificity exhibited by two of the more potent drugs now in clinical trials, it would be beneficial to use hydroxamates of greater enzyme specificity. This would be particularly the case if the hydroxamate inhibitors exhibited limited inhibition of MMP-1 that is relatively ubiquitous and as yet not associated with any pathological condition, while exhibiting quite high inhibitory activity against one or more of MMP-2, MMP-9 or MMP-13 that are associated with several pathological conditions.

Non-limiting examples of matrix metalloproteinase inhibitors that may be used in the present invention are identified in Table No. 1, below.

Table No. 1. Matrix metalloproteinase inhibitors.

Compound	Trade Name	Reference	Dosage
Biphenyl		WO 97/18188	
hydroxamate			
	AG-3067	Winter Conf.	
	(Agouron	Med. Bio-	
	Pharm.	organic	
	Inc.)	Chem. 1997	
		January, 26-	
		31	·
	AG-3340	WO 97/20824	50 mg/kg
	(Agouron		treatment
	Pharm.		of Lewis
	Inc.)		lung
			carcinomas
			in test
			animals
	AG-2024		
	(Agouron		
	Pharm.		
	Inc.)		:
	AG-3365		
	(Agouron		
	Pharm.		
	Inc.)		
3(S)-N-hydroxy-		WO 97/20824.	In female
4-(4-[4-		FEBS (1992)	Lewis rats,
(imidazol-1-		296 (3):263	arthritis
yl)phenoxy]benze			model: dose
nesulfonyl)-2,2-			of 25

Compound	Trade Name	Reference	Dosage
dimethyl-			mg/kg/day
tetrahydro-2H-			gave 97.5%
1,4-thiazine-3-			weight loss
carboxamide, and			inhibition
derivatives			
thereof			
Heteroaryl		WO 98/17643	
succinamides			
derivatives			
	AG-3296		
	(Agouron		
	Pharm.		
<u>.</u>	Inc.)		
	AG-		
	3287 (Agour		
	on Pharm.		
	Inc.)		
	AG-3293		
	(Agouron		
	Pharm.		
	Inc.)		
	AG-3294		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
	(Agouron		
٠	Pharm.		
	Inc.)		
	AG-3067	Winter Conf	
	(Agouron	Med Bio-	
	Pharm.	organic Chem	
	Inc.)	1997 January	
		26-31	

Compound	Trade Name	Ref rence	Dosage
2R,4S)-4-		EP 0818443	Dosage
hydroxy-2-		EF 0010443	1
isobutyl-5-			
mercapto-N-			
[(1S)-2,2-	-		÷
dimethyl-1-			
methylcarbamoylp			
ropyl]			
pentanamide			
N-alkyl, N-		WO 98/16520	
phenylsulfonyl-			:
N'-hydroxamic			
acid derivatives			
of heteroaryl			
carboxylic acids			
Novel N-alkyl,		WO 98/16514	
N-			
phenylsulfonyl-		,	
N`-hydroxamic			
acid derivatives			
of heteroaryl			
carboxylic acids			
Novel N-alkyl,		WO 98/16506	
N-			
phenylsulfonyl-			
N`-hydroxamic			
acid derivatives			
of cycloalkane			
carboxylic acids			
Novel N-alkyl,		WO 98/16503	

Compound	Trade Name	Reference	Dosage
N-			
phenylsulfonyl-			
N`-hydroxamic			
acid derivatives			
of anthranilic			
acid			
sulfonamido-		EP 03/98753	
hydroxamic acid			, · ·
derivatives			
TIMP-3:		WO 95/09918	· · · · · · · · · · · · · · · · · · ·
polynucleotides			
encoding			
endogenous			
(human) peptides			
(3alpha,		WO 93/23075	,
5beta,6alpha,7al			
phabeta)-4`,4`-			
(hexahydro-2,2-			
dimethyl-1,3-			
benzodioxole-5,			
6-diyl)bis(2,6-	·		
piperazinedione)			
and derivatives			
thereof			
	BE-16627B	WO 91/08222.	
		Int. J.	
		Cancer 1994	
		58 5 730 -	
		735	
(25)-4-(4-(4-		WO 96/15096	

Compound	Trade Name	Reference	Dosage
chlorophenyl)phe			
nyl)-4-oxo- 2-			
(2-			
phthalimidoethyl			
)butanoic acid	-		
	Bay-12-	WO 96/15096	10 to 400
	9566		mg/day
4-oxo-2-(2-		WO 97/43238	
phthalimidoethyl			
) alkanoic acid			
derivatives			
Novel 4-(4-	-	WO 97/43237	
Alkynylphenyl)			
4-oxobutanoic			
acid derivatives			·
Substituted 4-		WO 96/15096	
biarylbutyric or			
5-			
biarylpentanoic			
acids and			
derivatives			
Substituted 4-		WO 98/22436	
biphenyl-4-			
hydroxybutyric			
acid derivatives			
2R,S)-HONH-CO-		J Med Chem	
CH(i-Bu)-CO-Ala-		1998 41 3	
Gly-NH2,		339 -345	
batimastat; BB-		WO 90/05719	15 to 135
94; Hydroxamic			mg/m2

Compound	Trade Name	Reference	Dosage
acid based			administer-
collagenase			ed intra-
inhibitors			pleurally
Hydroxamic acid		WO 90/05719	
based			
collagenase			
inhibitors			,
marimastat BB-		WO 94/02447	5 to 800 mg
2516; Hydroxamic			daily
acid derivatives			
alpha-cycloalkyl		Bio-organic	
analogs of		Med Chem	
marimastat		Lett 1998 8	
		11 1359 -	
		1364	
	GI-245402		
	(BB-2983)		
Hydroxamic acid		WO 94/21625	
derivatives			!
Succinyl		WO 95/32944	
hydroxamic acid,	·		
N-formyl-N-			
hydroxy amino			
carboxylic acid			
and succinic			
acid amide			
derivatives			
hydroxamic acid,		WO 97/19053	
N-formyl-N-			
hydroxyamino and			

carboxylic acid derivatives, pseudopeptide hydroxamic and carboxylic acid		WO 97/19050	
pseudopeptide hydroxamic and		WO 97/19050	
hydroxamic and		WO 97/19050	ļ
carboxylic acid			
JULION LEG ACIA			
derivatives from			
the			
corresponding			
lactone and			
alpha-amino acid			
Succinic acid		WO 97/03966.	
amide		GB 95/00111.	
derivatives		GB 95/00121.	
Hydroxamic acid		WO 97/02239	
derivatives			:
Succinamidyl		WO 96/33165	
(alpha			
substituted)			
hydroxamic acid			
derivatives			
(2S,3R)-3-[2,2-		WO 96/25156	
dimethyl-1S-			
(thiazol-2-	·		
ylcarbamoyl)pro-			
pylcarbamoyl]-5-			
methyl-2-(prop-			l
2-enyl)hexano-		·	
hydroxanic acid			
and derivatives			
thereof			

Compound	Trade Name	Reference	Dosage
Hydroxamic or		WO 96/16931	
carboxylic acid			
derivatives	,		
hydroxamic and		WO 96/06074	
carboxylic acids			
2-[(1S)-1-((1R)-		WO 98/23588	
2-[[1,1`-			
biphenyl]-4-			
ylmethylthio]-1-			
[(1S)-2,2-			
dimethyl-1-			
(methylcarbamoyl			
)propylcarbamoyl			
]ethylcarbamoyl)			
-4-(1,3-dioxo-			
1,3-			•
dihydroisoindol-			
2-yl)butylthio]-			
acetate, and			
derivatives		,	
thereof	·		
Hydroxamic acid		WO 95/09841	
derivatives as			
inhibitors of			
cytokine			
production			
Hydroxamic acid		WO 94/24140	
derivatives			
Aromatic or		WO 95/19956	
heteroaryl			

Compound	Trade Name	Reference	Dosage
substituted			
hydroxamic or			
carboxylic acid			
derivatives			
Hydroxamic acid		WO 95/19957	Doses are
derivatives			preferably
			1 to 100
			mg/kg.
Hydroxamic acid		WO 95/19961	Doses are
and carboxylic			preferably
acid derivatives			1 to 100
			mg/kg.
Butanediamide,	BB-1433		At 50 mg/kg
N1-			bid. p.o.
[1(cyclohexyl-			inhibited
methyl)-2			bone
(methylamino)-2-			mineral
oxoethyl]-N4,3-			density
dihydroxy-2-(2-			loss
methylpropyl)-,			
[2R[N1(S*),2R*,3	·		
S*]]-			
tetracycline		EP 733369	D-penicill-
analogs and D-			amine
penicillamine			reduced
			allergic
			encephaliti
			s symptom
			scores in a
			dose

Compound	Trade Name	Reference	Dosage
			dependent
			manner at
			27, 125 and
			375 mug
			with
			complete
} 			inhibition
	CDP-845	Biochem	
		Pharmacol	
		1990 39 12	
		2041-2049	
succinamide		WO 95/04033	oral
derivatives			bioavail-
			ability by
			murine
			pleural
			cavity
			assay in
			the
			presence of
			gelatinase:
			Between 73%
			and 100%
			inhibition
			was
			displayed
			at 10 mg/kg
			for six of
			the
			compounds.
L			

Compound	Trade Name	Reference	Dosage
			The seventh
	,		displayed
•			100%
	9/1		inhibition
			at 80
		v	mg/kg.
Peptidyl		WO 94/25435.	
derivatives		WO 94/25434	
Mercaptoalkyl-		WO 97/19075	
peptidyl			
compounds having			
an imidazole			
substituent			
mercaptoalkyl-		WO 97/38007.	
peptide		WO 95/12389.	
derivatives		WO 96/11209.	
Mercaptoalkyl-		WO 97/37974	
amide			
derivatives			
arylsulfonyl-		WO 97/37973.	
hydrazine	,	WO 95/12389	
derivatives			
N-acetylthio-		WO 96/35714	
lacetyl-N-(3-			
phthalimidopropy			
1)-L-leucyl-L-			
phenylalanine N-			
methylamide			
2-acetylsulfany-		WO 96/35712	dosages of
1-5-phthalimido-			about 0.5

Compound	Trade Name	Reference	Dosage
pentanoyl-L-			mg to 3.5 g
leucineN-(2-			per day for
phenylethyl)-			the
amide			treatment
·			of inflam-
			mation
5-phthalimido-		WO 96/35711	
pentanoyl-L-			
leucyl-L-			
phenylalanineN-			
methylamide			
peptidyl		WO 98/06696	
derivatives			
4-[4-		WO 98/05635	
(methoxycarbonyl			
methoxy)-3,5-			
dimethylphenyl]-			
2-methyl-1(2H)-			
phthalazinone,			
and hydroxamic			
and carboxylic			
acid derivatives			
thio-substituted	,,,,	WO 97/12902	
peptides			
Mercaptoamides		WO 97/12861	
Peptidyl		WO 96/35687	
derivatives			
having SH or			
acylo groups			
which are			

Compound	Trade Name	Reference	Dosage
amides, primary			
amides or			
thioamides			
	D-5410		
	(Chiro-		
	science		
	Group plc)		
		WO 95/13289	
	CH-104,		
	(Chiro-		·
	science		
	Group plc)		
	D-2163		
	(Chiro		
	Science		
	Ltd.)		
	D-1927		
	(Chiro		
	Science		
•	Ltd.)		
	Dermastat		
	(Colla-		
	Genex		
	Phar-		
	maceu-		
	tical		
	Inc.)		
	Metastat	,	
	(Colla-		
	Genex)		

Compound	Trade Name	Reference	Dosage
	Osteostat		
	(Colla-		
	Genex		
	Phar-		
	maceu-		
	tical		
	Inc.)		
	doxy-		Gingival
	cycline;		crevicular
	Roche;	;	fluid
	Periostat		collagenase
			is reported
			to be
	Ę		inhibited
			at
			concentra-
			tions of 5-
			10 microg
			/ml or 15-
			30 microM
2S, 5R, 6S-3-		WO 97/18207	
aza-4-oxo-10-			
oxa-5-isobutyl-			
2-(N-			
methylcarbox-			
amido)-			
[10]paracyclopha			
ne-6-N-			
hydroxycarboxami			
đe			

Compound	Trade Name	Reference	Dosage
hydroxamic acid		WO 96/33176	
and amino-			
carboxylate			
compounds			
N-hydroxamic		WO 96/33166	
derivatives of			
succinamide			
Macrocyclic		J Med Chem	
amino		1998 41 11	
carboxylates		1749-1751	
	SE-205 (Du	Bio-organic	
	Pont Merck	Med Chem	
	Pharm Co.)	Lett 1998 8	
		7 837-842.	
		J Med Chem	·
		1998 41 11	
		1745 -1748	
macrocyclic			
matrix	:		
metalloprotease-			
8 inhibitors			
Hydroxamic acid		WO 95/22966	
and carboxylic			
acid derivatives			
succinamid		US 5256657	
derivatives			
mercaptosulfide		WO 95/09833	
derivatives			
sulfoximine and		WO 95/09620	
sulfodiimine			

Compound	Trade Name	Reference	Dosage
derivatised			
peptides			
water soluble		WO 96/33968	
MMP inhibitors			
hydantoin		EP 06/40594	
derivatives			
Piperazine		WO 98/27069	
derivatives			
	GI-155704A	J Med Chem	
		1994 37 5	
		674.	
		Bioorganic	
		Med Chem	
		Lett 1996 6	
		16 1905 -	
		1910	
Cyclic imide		EP 05/20573	
derivatives.			
3-(mercapto-		WO 97/48685	
methyl) hexa-			
hydro-2,5-	·		
pyrazinedione			
derivatives			
beta-		WO 96/40738	
mercaptoketone			
and beta-			
mercaptoalcohol			
derivatives			
	ilomastat	US 5114953.	eye drops
	MPI; GM-	Cancer Res	containing

Compound	Trade Name	Reference	Dosage
	6001;	1994 54 17	ilomastat
	Galardin	4715-4718	(800
			microg/ml)
Cyclic and		WO 97/18194	
heterocyclic N-			
substituted			
alpha-			
iminohydroxamic			
and carboxylic			
acids			
Aminomethyl-		EP 703239	
phosphonic and			
aminomethyl-			
phosphinic acids			
derivatives			
3-Mercapto-		WO 98/12211	
acetylamino-1,5-			
substituted-2-			
oxo-azepan			
derivatives			
2-substituted		WO 94/04531	
indane-2-			
mercaptoacetyl-			
amide tricyclic			
derivatives			
- <del>1</del>	Ro-2756		
	(Roche		
	Holding		
	AG)		
	Ro-26-4325		

Compound	Trade Name	Reference	Dosage
	(Roche		
,	Holding		
	AG)		
	Ro-26-5726		
	(Roche		
	Holding		
	AG)		
	Ro-26-6307		
	(Roche		
	Holding		·
	AG)		
	Ro-31-9790	J Am Soc	mono-
	(Roche	Nephrol 1995	arthritis
	Holding	6 3 904.	in rat: 100
	AG)	Inflamm Res	mg/kg/day
		1995 44 8	
		345 -349	
substituted and		WO 92/09556	
unsubstituted			
hydroxamates			
(specifically N-	·		
[D,L-2-isobutyl-			
3-(N'-hydroxy-			
carbonyl-amido)-			
propanoyl]trypto			
phanmethylamide)			
GM6001, N-(2(R)-		WO 95/24921	
2 -			
(hydroxyaminocar			
bonylmethyl)-4-			

Compound	Trade Name	Reference	Dosage
methylpentanoyl)			
-L-tryptophan			
methylamide.			
Oligonucleotice			
(c-jun)			
Sulfated		WO 98/11141	
polysaccharides			
	KB-R7785;	Life Sci	
	KB-R8301;	1997 61 8	
	KB-R8845	795-803	
Fas ligand		WO 97/09066	
solubilization			
inhibitor			
gelastatin AB,			
KRIBB			
	KT5-12	Faseb J 1998	
	(Kotobuki	12 5 A773	
	Seiyaku Co	(4482)	
	Ltd.)		
2-(N2-[(2R)-2-		GB 23/18789	
(2-hydroxyamino-			
2-oxoethyl)-5-			
(4-			
methoxyphenoxy)p			
entanoyl]-L-			
phenylalanylamin			
o)ethanesulfonam		·	
ide, and			
carboxylic acid			
derivatives			

Compound	Trade Name	Reference	Dosage
thereof			
Chromone		EP 758649	2-
derivatives			Pyrolylthio
			-chromone
e e e e e e e e e e e e e e e e e e e			in a murine
			melanoma
			model
			produced
			37%
		•	inhibition
			at 100
			mg/kg
Esculetin		EP 719770	
derivatives,			
substituted and		WO 92/09563	
unsubstituted			
hyroxyureas and			
reverse			
hydroxamates			
Synthetic MMP		WO 94/22309	
inhibitors (ex.	-		
N-(D,L-2-			
isobuty1-3-(N'-			
hydroxycarbonyla			
mido)propanoyl)t			
ryptophan			
methylamide)			
Reverse	-,	WO 95/19965	in female
hydroxamates and			mice
hydroxyureas			infected

w/murimeland init 8 g foll by 150 mg/kg/ N- (mercaptoacyl)- aryl derivatives of leucine and phenylalanine N-carboxyalkyl derivatives Substituted cyclic derivatives  GB 22/82598 Inflam n is s to be effect treate oral	
init 8 g fold by 150 mg/kg/ N- (mercaptoacyl)- aryl derivatives of leucine and phenylalanine N-carboxyalkyl derivatives Substituted cyclic derivatives  GB 22/82598 Inflam n is s to be effect treate	
g follow 150 mg/kg/ N- (mercaptoacyl)- aryl derivatives of leucine and phenylalanine N-carboxyalkyl derivatives Substituted cyclic derivatives  GB 22/82598 Inflam n is so to be effect treate	oma -
g follow 150 mg/kg/ N- (mercaptoacyl)- aryl derivatives of leucine and phenylalanine N-carboxyalkyl derivatives Substituted cyclic derivatives  GB 22/82598 Inflam n is so to be effect treate	30 mu
by 150 mg/kg/ N- (mercaptoacyl)- aryl derivatives of leucine and phenylalanine N-carboxyalkyl derivatives  Substituted cyclic derivatives  GB 22/82598 Inflam n is s to be effect treate	
N- (mercaptoacyl)- aryl derivatives of leucine and phenylalanine  N-carboxyalkyl derivatives  Substituted cyclic derivatives  GB 22/82598 Inflam n is s to be effect treate	
(mercaptoacyl) -   aryl derivatives   of leucine and   phenylalanine   N-carboxyalkyl   derivatives   Substituted   cyclic   derivatives   GB 22/82598   Inflam   n is s   to be   effect   treate	day
aryl derivatives of leucine and phenylalanine  N-carboxyalkyl derivatives  Substituted cyclic derivatives  GB 22/82598 Inflam n is s to be effect treate	·
of leucine and phenylalanine  N-carboxyalkyl WO 95/29689  derivatives  Substituted GB 22/82598 Inflamory to be effect treated	
phenylalanine  N-carboxyalkyl derivatives  Substituted cyclic derivatives  GB 22/82598 Inflam n is s to be effect treate	
N-carboxyalkyl derivatives  Substituted cyclic derivatives  GB 22/82598 Inflam n is s to be effect treate	
derivatives  Substituted  Cyclic  derivatives  GB 22/82598  Inflam  n is s  to be  effect  treate	
Substituted GB 22/82598 Inflam cyclic n is s derivatives to be effect treate	
cyclic derivatives to be effect treate	
derivatives to be effect treate	matio
effect	tated
treate	
	ively
oral	d by
admini	strat
ion of	0.01
to 50	mg/kg
Substituted n- GB 22/72441	
carboxyalkyldi-	
peptides	
(2S, 4R) -2- WO 97/11936	
methyl-4-	
(phenylamino-	
carbonylmethyl-	;
aminocarbonyl)-	

Compound	Trade Name	Reference	Dosage
6-(4-propyl-			
phenyl)hexanoic			
acid, and			
carboxylic acid			
derivatives			
Substituted		US 5403952	
cyclic			
derivatives			
Thiol		WO 98/03166	
sulfonamide			
metalloprotease			
inhibitors			
Thiol sulfone		WO 98/03164	
metalloprotein-			
ase inhibitors			•
formulations		WO 97/47296	
containing			
vanadium			
compounds and N-			
acetylcysteine			
	NSC-		
	683551;		<u> </u>
	COL-3		
	(National		
	Cancer		
	Institute)		
	BB-3644		
	(Neures		
	Ltd.)		
Arylsulfonamido-	CGS-	Int Congr	600 mg tid

Compound	Trade Name	Reference	Dosage
substituted	27023A;	Inflamm Res	(Ph I -
hydroxamic acids	CGS-25966	Assoc 1994	colorectal
		7th Abs 73.	and
		EP-00606046	melanoma
		·	patients);
			100 mg/kg
			in food in
			osteoarthri
			tis model
			rabbits
alpha-		WO 97/22587	
Substituted			
arylsulfonamido			
hydroxamic acid			
derivatives			·
Arylsulfonamido-		US 5455258	active at
substituted			30 mg/kg in
hydroxamic acids			in vivo
			assay
Arylsulfonamido-		WO 96/00214	
substituted	·		
hydroxamic acids			
2S,3S)-N-		WO 98/14424	·
hydroxy-5-			
methyl-2-[2-(2-			
methoxyethoxy)et			
hoxymethyl]-3-			
(N-[(1S)-1-(N-			
methylcarbamoyl)			
-2-			

Compound	Trade Name	Reference	Dosage
phenylethyl]carb			
amoyl)hexanamide			
and Hydroxamic	·		
acid deriva-			
tives	;		
arylsulfonamido-		WO 96/40101	in tumor
substituted			model mice:
hydroxamic acids			administere
			d for 7 to
			17 days at
			a dosage of
			30 mg/kg
			twice daily
Aryl (sulfide,		WO 97/49679	
sulfoxide and	:		·
sulfone)			
derivatives			
Phenylsulfon-		WO 97/45402	
amide			
derivatives			
Arylsulfonamido-		EP 757037	
aminoacid			
derivative			
A1PDX (Oregon			
Health Sciences			
University)			
futoenone		Bio-organic	
analogs		Med Chem	
		Lett 1995 5	
		15 1637 -	

WO 00/37107

Compound	Trade Name	Reference	Dosage
		1642	
debromohymeni-		WO 96/40147	preferred
aldisine and			1-30 mg/day
related			
compounds			
amide		WO 96/40745	
derivatives of			
5-amino-1,3,4-			
thiadiazolones			
3S-(4-(N-		WO 94/21612	
hydroxylamino)-			
2R-			
isobutylsuccinyl			
)amino-1-			
methoxymethyl-			
3,4-			
dihydrocarbostyr			
il and			
deriviatives			
therof			
Carbostyryl		JP 8325232	
derivatives			
OPB-3206 (Otsuka			
Pharmaceutical			
Co, Ltd.)			
Arylsulfonyl		WO 96/33172	
hydroxamic acid			
derivatives			
Cyclic sulfone		EP 818442	
derivatives			

Compound	Trade Name	Reference	Dosag
arylsulfonamido		WO 96/27583	
N-hydroxamic			
acid derivatives			ļ
of butyric acid			
Arylsulfonyl-		WO 98/07697	
amino hydroxamic			
acid derivatives			
phosphinate-		WO 98/03516	
based			
derivatives			
cyclopentyl-		WO 92/14706	
substituted			
glutaramide			
derivatives			
N-hydroxamic		WO 97/49674	
acid succinamide			
derivatives			
Thiadiazole		WO 97/48688	
amide MMP			
inhibitors.			
(S)-1-[2-		WO 97/40031	
[[[(4,5-Dihydro-			
5-thioxo-1,3,4-			
thiadiazol-2-			
yl)amino]-			
carbonyl]amino]-			
1-oxo-3-			
(pentafluoro-			
phenyl)propyl]-			
4-(2-pyridinyl)-			

Compound	Trade Name	Reference	Dosage
piperazine			
hydroxamic acid		WO 97/32846	
derivatives of	;		
pyrrolidone-3-			
acetamide.			
alpha-		WO 98/17645	
arylsulfonamido-			
N-hydroxamic			
acid derivatives			
beta-		WO 98/13340	·
Sulfonylhydrox-			
amic acids			
Hydroxamic acid		US 5712300	
derivatives			
	PNU-99533		
	(Pharmacia		
	& UpJohn		
	Inc.)		
	PNU-143677		
	(Pharmacia		
	& UpJohn		
	Inc.)		
	POL-641		
	(Poli-		
	farma)		
Peptidomimetic		WO 96/20,18.	
inhibitors		WO 96/29313.	
		WO 98/08814.	
		WO 98/08815.	
		WO 98/08850.	

Compound	Trade Name	Reference	Dosage
		WO 98/08822.	
`.		WO 98/08823.	
·		WO 98/08825.	
		WO 98/08827.	
2R) -N-	()-caprol-	WO 96/29313	rheumatoid
hydroxycarboxami	actam-		arthritis:
demethyldecanoic	(3S)-amine		female
acid amide of			subject -
1N-			50 mg po
(carbomethoxy-			for 2 yrs;
methyl)			male ·
			subject -
			70 mg po
			daily for 5
			yrs;
!			corneal
			ulcer:
			male
			subject 0
			10 mg in
			saline soln
			for 2
			months, 2
			times/day
3-(N-[(N-		WO 96/20918	
Hydroxyaminocarb	1		
onyl)methyl]-N-			
isobutylaminocar			ļ
bonyl) -2-(R)-			
isobutylpro-			

Compound	Trade Name	Reference	Dosage
panoyl-L-			
phenylalanine			
amide			
N-hydroxy-		WO 98/08853	
phosphinic acid			
amides		·	
N'-arylsulfonyl		WO 98/08850	
derivatives of			
spirocyclic-N-			
hydroxycarbox-			
amides			
N`-arylsulfonyl		WO 98/08827	
derivatives of			
thiazepinone and			
azepinone-N-			
hydroxycarbox-			
amides	:		
Substituted		WO 98/08825	
piperazine			
derivatives			
N'-arylsulfonyl		WO 98/08823	
derivatives of			
pyrimidine,			
thiazepine and			
diazepine-N-			
hydroxycarbox-			
amides			
Substituted		WO 98/08815	
pyrrolidine			
derivatives			

Compound	Trade Name	Reference	Dosage
Substituted		WO 98/08814	
heterocycles			
Substituted 1,3-		WO 09/08822	
diheterocyclic			
derivatives			!
substituted 5-		WO 98/25949	
amino-1,2,4-			
thiadiazole-2-			
thiones			
Hydroxamic acid		WO 97/24117	· · · · · · · · · · · · · · · · · · ·
derivatives			
which inhibit			
TNF production.			
6-methoxy-		WO 97/37658	
1,2,3,4-			·
tetrahydro-			
norharman-1-			
carboxylic acid			
	RS-130830	Arthritis	
		Rheum 1997	
		40 9 SUPPL.	
		S128	
Aralkyl MMP		WO 96/16027	
inhibitors (ex.			
N-(2R-			
carboxymethyl-5-			
(biphen-4-			
yl)pentanoyl)-L-			
t-butylglycine-			
N'-(pyridin-4-			

Compound	Trade Name	Reference	Dosage
yl)carboxamide)			
	Ro-32-3555		
	(Roche		
	Holding		
	AG)		
	Ro-32-1278		
	(Roche		
	Holding		
	AG)		
	Ro-32-1541		
	(Roche		
	Holding	,	
	AG)		
······································	Ro-31-3790		Arthritic
	(Roche		model rats:
	Holding		Protection
	AG)		of
			cartilage
			degradation
			following
	. · ·		oral
			administrat
			ion; ED50 =
			10 mg/kg po
(3R,11S)-N-		WO 95/04735	
hydroxy-5-			
methyl-3-(10-			
oxo-1,9-			
diazatricyclo-			
(11.6.1.014,19)e			

Compound	Trade Name	Reference	Dosage
icosa-			
13(20),14(19),15			
,17-tetraen- 11-			
ylcarbamoyl)hexa			
namide and			
derivatives			
thereof			
Bridged indoles		WO 96/23791	
(Roche Holding			
AG)			
substituted	<del> </del>	EP 780386	
phenylsulfonyl			
acetamide,			
propionamide and			
carboxamide			
compounds			
5-(4'-biphenyl)-		WO 97/23465	
5-[N-(4-			
nitrophenyl)			
piperazinyl]			
barbituric acid	·		
Malonic acid		EP 716086	
based matrix			
metalloproteinas			
e inhibitors			
phenyl		WO 95/12603	
carboxamide			
derivatives			
Malonic acid		EP 716086	
based mmp			

Compound	Trade Name	Reference	Dosage
inhibitors			
(specifically 2-			
(4-acetylamino-			
benzoyl)-4-			
methylpentanoic	<del>,</del>		-
acid)	i		
Hydroxyl amine	Ro-31-	EP 236872	
derivatives	4724; Ro-		
	31-7467;		

The following individual patent references listed in Table No. 2 below, hereby individually incorporated by reference, describe various MMP inhibitors suitable for use in the present invention described herein, and processes for their manufacture.

Table No. 2. MMP inhibitors

10

EP	189784	US 4609667	WO 98/25949	WO 98/25580
JP	10130257	WO 98/17655	WO 98/17645	US 5760027
US	5756545	WO 98/22436	WO 98/16514	WO 98/16506
WO	98/13340	WO 98/16520	WO 98/16503	WO 98/12211
WO	98/11908	WO 98/15525	WO 98/14424	WO 98/09958
WO	98/09957	GB 23/18789	WO 98/09940	WO 98/09934
JР	10045699	WO 98/08853	WO 98/06711	WO 98/05635
WO	98/07742	WO 98/07697	WO 98/03516	WO 98/03166
WO	98/03164	GB 23/17182	WO 98/05353	WO 98/04572
wo	98/04287	WO 98/02578	WO 97/48688	WO 97/48685

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WO 97/49679	WO 97/47599	WO 97/43247	WO 97/43240
WO 97/43238	EP 818443	EP 818442	WO 97/45402
WO 97/40031	WO 97/44315	WO 97/38705	US 5679700
WO 97/43245	WO 97/43239	WO 97/43237	JP 09227539
WO 97/42168	US 5686419	WO 97/37974	WO 97/36580
WO 97/25981	WO 97/24117	US 5646316	WO 97/23459
WO 97/22587	EP 780386	DE 19548624	WO 97/19068
WO 97/19075	WO 97/19050	WO 97/18188	WO 97/18194
WO 97/18183	WO 97/17088	DE 19542189	WO 97/15553
WO 97/12902	WO 97/12861	WO 97/11936	WO 97/11693
WO 97/09066	JP 09025293	EP 75/8649	WO 97/03966
WO 97/03783	EP 75/7984	WO 97/02239	WO 96/40745
WO 96/40738	WO 96/40737	JP 08/311096	WO 96/40204
WO 96/40147	WO 96/38434	WO 96/35714	WO 96/35712
WO 96/35711	WO 96/35687	EP 74,3,070	WO 96/33968
WO 96/33165	WO 96/33176	WO 96/33172	WO 96/33166
WO 96/33161	GB 23/00190	WO 96/29313	EP 73/6302
WO 96/29307	EP 733369	WO 96/26223	WO 96/27583
WO 96/25156	GB 22/98423	WO 96/23791	WO 96/23505
GB 22/97324	DE 19501032	WO 96/20918	US 5532265
EP 719770	WO 96/17838	WO 96/16931	WO 96/16648
WO 96/16027	EP 716086	WO 96/15096	JP 08104628
WO 96/13523	JP 08081443	WO 96/11209	EP 703239
WO 96/06074	WO 95/35276	WO 96/00214	WO 95/33731
WO 95/33709	WO 95/32944	WO 95/29892	WO 95/29689
CA 21/16924	WO 95/24921	WO 95/24199	WO 95/23790
WO 95/22966	GB 22/87023	WO 95/19965	WO 95/19961
WO 95/19956	WO 95/19957	WO 95/13,289	WO 95/13380
WO 95/12603	WO 95/09918	WO 95/09841	WO 95/09833
WO 95/09620	WO 95/08327	GB 22/82598	WO 95/07695
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WO 95/05478	WO 95/04735	WO 95/04033	WO 95/02603
WO 95/02045	EP 626378	WO 94/25435	WO 94/25434
WO 94/21612	WO 94/24140	WO 94/24140	EP 622079
WO 94/22309	JP 06256209	WO 94/21625	FR 27/03053
EP 606046	WO 94/12169	WO 94/11395	GB 22/72441
WO 94/07481	WO 94/04190	WO 94/00119	GB 22/68934
WO 94/02446	EP 575844	WO 93/24475	WO 93/24449
US 5270326	US 5256657	WO 93/20047	WO 93/18794
WO 93/14199	WO 93/14096	WO 93/13741	WO 93/09090
EP 53/2465	EP 532156	WO 93/00427	WO 92/21360
WO 92/09563	WO 92/09556	EP 48/9579	EP 489577
US 5114953	EP 45/5818	US 5010062	AU 90/53158
WO 97/19075	US 7488460	US 7494796	US 7317407
EP 277428	EP 23/2027	WO 96/15096	WO 97/20824
US 5837696			

The Marimastat used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 94/02,447.

The Bay-12-9566 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 96/15,096.

The AG-3340 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 97/20,824.

The Metastat used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,837,696.

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The D-2163 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 97/19,075.

More preferred zinc matrix metalloproteinase

inhibitors include those described in the individual
U.S. Patent applications, PCT publications and U.S.

Patents listed below in Table No. 3, and are hereby individually incorporated by reference.

## 10 Table No. 3. More preferred zinc matrix metalloproteinase inhibitors

U.S. Patent	Application	Serial	Number	97/12,873
U.S. Patent	Application	Serial	Number	97/12,874
U.S. Patent	Application	Serial	Number	98/04,299
U.S. Patent	Application	Serial	Number	98/04,273
U.S. Patent	Application	Serial	Number	98/04,297
U.S. Patent	Application	Serial	Number	98/04,300
U.S. Patent	Application	Serial	Number	60/119,181
WO 94/02447				
WO 96/15096				
WO 97/20824				
WO 97/19075				
US 5837696				

Even more preferred zinc matrix metalloproteinase inhibitors that may be used in the present invention include:

M1)

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride;

M2)

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1-cyclopropyl-N-hydroxy-4-[[4-[4(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride;

-82-

M3)

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1piperidinyl]sulfonyl]-4-piperidinecarboxamide

M4)

monohydrochloride;

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N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide dihydrochloride;

-83-

M5)

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1piperidinyl]sulfonyl]benzamide;

M6)

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N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

M7)

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

M8)

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N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

15 9)

-85-

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]-N1,2 -dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-);

5 M10)

Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]- 4-yl)oxy]-2[(phenylthio)methyl]butanoic acid;

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M11)

Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2 dimethyl- 4-[[4-(4-pyridinyloxy)phenyl]- sulfonyl]- 3-thiomorpholinecarboxamide;

M12) CollaGenex Pharmaceuticals CMT-3 (Metastat),6- demethyl-6-deoxy-4-dedimethylaminotetracycline;

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-86-

M13) Chiroscience D-2163, 2- [1S- ([(2R,S)-acetylmercapto-5-phthalimido]pentanoyl-L-leucyl)amino-3-methylbutyl]imidazole;

5 M14

N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride;

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M15)

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4 (trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride; -87-

M16)

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinearboxamide;

M17)

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1-cyclopropyl-N-hydroxy-4-[[4-[4-10 (trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride; -88-

M18)

4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride;

M19)

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4-[[4-(4-

10 chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide;

M20)

N-hydroxy-4-[[4-(4methoxyphenoxy)phenyl)sulfonyl]-1-(2propynyl)-4-piperidinecarboxamide;

-89-

'M21)

1-cyclopropyl-4-[[4-[(4-

fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-

4-piperidinecarboxamide;

M22)

10 1-cyclopropyl-N-hydroxy-4-[[4-

(phenylthio)phenyl]sulfonyl]-4-

piperidinecarboxamide;

M23)

15

tetrahydro-N-hydroxy-4-[[4-(4pyridinylthio)phenyl]sulfonyl]-2H-pyran-4carboxamide;

-90-

M24)

tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2Hpyran-4-carboxamide.

Still more preferred MMP inhibitors include:

M1)

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N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M2)

1-cyclopropyl-N-hydroxy-4-[[4-[4(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride;

M3)

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N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride; -92-

M4)

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide dihydrochloride;

M5)

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N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1piperidinyl]sulfonyl]benzamide;

-93-

M6)

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide dihydrochloride;

M7)

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N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-10 (trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide dihydrochloride;

-94-

M8)

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M9)

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British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]N1,2 -dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-);

M10)

Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'iphenyl]- 4-yl)oxy]-2[(phenylthio)methyl]butanoic acid;

M11)

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Agouron Pharmaceuticals AG-3340, N-hydroxy
2,2- dimethyl- 4-[[4-(4pyridinyloxy)phenyl]sulfonyl]- 3thiomorpholinecarboxamide;

M12) CollaGenex Pharmaceuticals CMT-3 (Metastat),

6- demethyl-6-deoxy-4dedimethylaminotetracycline;

M13) Chiroscience D-2163, 2- [1S- ([(2R,S)20 acetylmercapto- 5- phthalimido]pentanoyl- Lleucyl)amino- 3- methylbutyl]imidazole.

-96-

The phrase "cyclooxygenase-2 inhibitor" or "COX-2 inhibitor" or "cyclooxygenase-II inhibitor" includes agents that specifically inhibit a class of enzymes, cyclooxygenase-2, with less significant inhibition of cyclooxygenase-1. Preferably, it includes compounds which have a cyclooxygenase-2 IC50 of less than about 0.2 µM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC50 of greater than about 1 µM, and more preferably of greater than 10 µM.

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Studies indicate that prostaglandins synthesized by cyclooxygenases play a critical role in the initiation and promotion of cancer. Moreover, COX-2 is overexpressed in neoplastic lesions of the colon, breast, lung, prostate, esophagus, pancreas, intestine, cervix, ovaries, urinary bladder, and head & neck. In several in vitro and animal models, COX-2 inhibitors have inhibited tumor growth and metastasis.

In addition to cancers per se, COX-2 is also expressed in the angiogenic vasculature within and adjacent to hyperplastic and neoplastic lesions indicating that COX-2 plays a role in angiogenesis. In both the mouse and rat, COX-2 inhibitors markedly inhibited bFGF-induced neovascularization. The utility of COX-2 inhibitors as chemopreventive, antiangiogenic and chemotherapeutic agents is described in the literature (Koki et al., Potential utility of COX-2 inhibitors in chemoprevention and chemotherapy. Exp. Opin. Invest. Drugs (1999) 8(10) pp. 1623-1638, hereby

incorporated by reference). Amplification and/or overexpression of HER-2/nue (ErbB2) occurs in 20-30% of human breast and ovarian cancers as well as in 5-15% of gastric and esophageal cancers and is associated with poor prognosis. Additionally, it has been recently discovered in vitro that COX-2 expression is upregulated in cells overexpressing the HER-2/neu oncogene. (Subbaramaiah et al., Increased expression of cyclooxygenase-2 in HER-2/neu-overexpressing breast cancer. Cancer Research (submitted 1999), hereby 10 incorporated by reference). In this study, markedly increased levels of PGE, production, COX-2 protein and mRNA were detected in HER-2/neu transformed mammary epithelial cells compared to a non-transformed partner 15 cell line. Products of COX-2 activity, i.e., prostaglandins, stimulate proliferation, increase invasiveness of malignant cells, and enhance the production of vascular endothelial growth factor, which promotes angiogenesis. Further, HER-2/neu induces the production of angiogenic factors such as vascular 20 endothelial growth factor.

Consequently, the administration of a COX-2 inhibitor in combination with an anti HER-2/neu antibodies such as trastuzumab (Herceptin®) and other therapies directed at inhibiting HER-2/neu is contemplated to treat cancers in which HER-2/neu is overexpressed.

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Also, it is contemplated that COX-2 levels are elevated in tumors with amplification and/or overexpression of other oncogenes including but not limited to c-myc, N-myc, L-myc, K-ras, H-ras, N-ras.

-98-

Products of COX-2 activity stimulate cell proliferation, inhibit immune surveillance, increase invasiveness of malignant cells, and promote angiogenesis. Consequently, the administration of a COX-2 inhibitor in combination with an agent or agents that inhibits or suppresses oncogenes is contemplated to prevent or treat cancers in which oncogenes are overexpressed.

Accordingly, there is a need for a method of treating or preventing cancer in a patient that overexpresses COX-2 and/or an oncogene. Methods for the production of anti- ErbB2 antibodies are described in WO 99/31140.

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Specific COX-2 inhibitors are useful for the treatment of cancer (WO98/16227) and in several animal models reduce angiogenesis driven by various growth factors (WO98/22101). Anti-angiogenesis was achieved with a COX-2 inhibitor in rats implanted with bFGF, vascular endothelium growth factor (VEGF) or carrageenan, proteins with well-known angiogenic properties. (Masferrer, et al., 89<sup>th</sup> Annual Meeting of the American Association for Cancer Research, March 1998.)

Pyrazoles can be prepared by methods described in WO 95/15,316. Pyrozoles can further be prepared by methods described in WO 95/15315. Pyrozoles can also be prepared by methods described in WO 96/03385. Thiophene analogs can be prepared by methods described in WO 95/00501. Preparation of thiophene analogs is also described in WO 94/15932. Oxazoles can be prepared by the methods described in WO 95/00501. Preparation of oxazoles is also described in WO 94/27980. Isoxazoles

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can be prepared by the methods described in WO 96/25405. Imidazoles can be prepared by the methods described in WO 96/03388. Preparation of imidazoles is also described in WO 96/03387. Cyclopentene cyclooxygenase-2 inhibitors can be prepared by the methods described in U.S. Patent No. 5,344,991. Preparation of cyclopentane Cox-2 inhibitors is also described in WO 95/00501. Terphenyl compounds can be prepared by the methods described in WO 96/16934. Thiazole compounds can be prepared by the methods described in WO 96/16934. Pyridine compounds can be prepared by the methods described in WO 96/03392. Preparation of pyridine compounds is also described in WO 96/24,585.

Nonlimiting examples of COX-2 inhibitors that may

15 be used in the present invention are identified in Table

No. 4 below.

Table No. 4. Cyclooxygenase-2 Inhibitors

Compound	Trade/	Reference	Dosage
	Research Name	<u> </u>	
1,5-Diphenyl-3-		WO 97/13755	
substituted	·		
pyrazoles			
	radicicol	WO 96/25928.	
		Kwon et al	
		(Cancer	
		Res(1992) 52	
		6296)	
	GB-02283745		
	TP-72	Cancer Res	
		1998 58 4	

Compound	Trade/	Reference	Dosage
	Research Name		
		717 -723	
1-(4-	A-183827.0		1
chlorobenzoyl)-3-			
[4-(4-fluoro-			
phenyl )thiazol-			
2-ylmethyl]-5-			
methoxy-2-methy			
lindole			
	GR-253035		
4-(4-cyclohexyl-	JTE-522	JP 9052882	<u> </u>
2-methyloxazol-5-			
yl)-2-			
fluorobenzenesulf			
onamide			
5-chloro-3-(4-			
(methylsulfonyl)p			
henyl)-2-(methyl-	,		
5-pyridinyl)-			
pyridine			
2-(3,5-difluoro-			
phenyl)-3-4-			
(methylsulfonyl)-			
phenyl)-2-	<b>!</b>		
cyclopenten-1-one			
	L-768277		
	L-783003		
	MK-966;	US 5968974	12.5-100 mg po
	VIOXX®		
indomethacin-		WO 96/374679	200 mg/kg/day

Compound	Trade/	Reference	Dosage
	Research Name		
derived			
indolalkanoic			
acid			
1-Methylsulfonyl-		WO 95/30656.	
4-[1,1-dimethyl-		WO 95/30652.	
4-(4-		WO 96/38418.	
fluorophenyl)cycl		WO 96/38442.	
openta-2,4-dien-			
3-yl]benzene			
4,4-dimethyl-2-			
pheny1-3-[4-			1
(methylsulfonyl)p			
henyl]cyclo-			
butenone			
2-(4-		EP 799823	
methoxyphenyl)-4-			
methyl-1-(4-			
sulfamoylphenyl)-			
pyrrole			
N-[5-(4-	RWJ-63556		
fluoro)phenoxy]th			
iophene-2-			
methanesulfon-			
amide			
5(E)-(3,5-di-	S-2474	EP 595546	
tert-butyl-4-			
hydroxy)benzylide			
ne-2-ethyl-1,2-			
isothiazolidine-			

Compound	Trade/	Reference	Dosage
	Research Name		
1,1-dioxide			
3-formylamino-7-	T-614	DE 38/34204	
methylsulfonylami			
no-6-phenoxy-4H-			
1-benzopyran-4-			
one			
Benzenesulfonamid	celecoxib	US 5466823	
e, 4-(5-(4-			
methylphenyl)-3-			
(trifluoromethyl)			
-1H-pyrazol-1-			
y1)-			
CS 502	(Sankyo)		
MK 633	(Merck)		
	meloxicam	US 4233299	15-30 mg/day
	nimesulide	US 3840597	

The following references listed in Table No. 5 below, hereby individually incorporated by reference, describe various COX-2 inhibitors suitable for use in the present invention described herein, and processes for their manufacture.

Table No. 5 COX-2 inhibitors

WO 99/30721	WO 99/30729	US 5760068	WO 98/15528
WO 99/25695	WO 99/24404	WO 99/23087	FR 27/71005
EP 921119	FR 27/70131	WO 99/18960	WO 99/15505
WO 99/15503	WO 99/14205	WO 99/14195	WO 99/14194
WO 99/13799	GB 23/30833	US 5859036	WO 99/12930
WO 99/11605	WO 99/10332	WO 99/10331	WO 99/09988

US	5869524	WO 99/05104	US 5859257	WO 98/47890
WO	98/47871	US 5830911	US 5824699	WO 98/45294
WO	98/43966	WO 98/41511	WO 98/41864	WO 98/41516
WO	98/37235	EP 86/3134	JP 10/175861	บร 5776967
WO	98/29382	WO 98/25896	ZA 97/04806	EP 84/6,689
WO	98/21195	GB 23/19772	WO 98/11080	WO 98/06715
WO	98/06708	WO 98/07425	WO 98/04527	WO 98/03484
FR	27/51966	WO 97/38986	WO 97/46524	WO 97/44027
WO	97/34882	US 5681842	WO 97/37984	US 5686460
WO	97/36863	WO 97/40012	WO 97/36497	WO 97/29776
WO	97/29775	WO 97/29774	WO 97/28121	WO 97/28120
WO	97/27181	WO 95/11883	WO 97/14691	WO 97/13755
WO	97/13755	CA 21/80624	WO 97/11701	WO 96/41645
WO	96/41626	WO 96/41625	WO 96/38418	WO 96/37467
WO	96/37469	WO 96/36623	WO 96/36617	WO 96/31509
WO	96/25405	WO 96/24584	WO 96/23786	WO 96/19469
WO	96/16934	WO 96/13483	WO 96/03385	US 5510368
WO	96/09304	WO 96/06840	WO 96/06840	WO 96/03387
WO	95/21817	GB 22/83745	WO 94/27980	WO 94/26731
WO	94/20480	WO 94/13635	FR 27/70,131	US 5859036
WO	99/01131	WO 99/01455	WO 99/01452	WO 99/01130
WO	98/57966	WO 98/53814	WO 98/53818	WO 98/53817
WO	98/47890	US 5830911	US 5776967	WO 98/22101
DE	19/753463	WO 98/21195	WO 98/16227	US 5733909
WO	98/05639	WO 97/44028	WO 97/44027	WO 97/40012
WO	97/38986	US 5677318	WO 97/34882	WO 97/16435
WO	97/03678	WO 97/03667	WO 96/36623	WO 96/31509
WO	96/25928	WO 96/06840	WO 96/21667	WO 96/19469
US	5510368	WO 96/09304	GB 22/83745	WO 96/03392
WO	94/25431	WO 94/20480	WO 94/13635	JP 09052882
L		<u> </u>	<del></del>	<del>`</del>

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GB	22/94879	WO 95/15316	WO 95/15315	WO 96/03388
WO	96/24585	US 5344991	WO 95/00501	US 5968974
US	5945539	US 5994381	-	

The celecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,466,823.

The valdecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,633,272.

The parecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,932,598.

The rofecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,968,974.

The Japan Tobacco JTE-522 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in JP 90/52,882.

Preferred COX-2 inhibitors that may be used in the present invention include, but are not limited to:

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C1)

$$H_2N$$
  $F$   $CH_3$ 

JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)2-fluorobenzenesulfonamide;

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C2)

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5pyridinyl)pyridine;

10 C3)

2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2cyclopenten-1-one;

15 C4)

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide;

-106-

C5)

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3phenyl-2(5H)-furanone;

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C6)

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;

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C7)

N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide;

-107-

C8)

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide;

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C9)

C10)

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C11)

6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone;

-108-

C12)

N-(4-nitro-2-phenoxyphenyl)methanesulfonamide;

5

C13)

$$CI$$
 $O$ 
 $OC_2H_5$ 
 $CF_3$ 

C14)

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3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone;

-109-

C15)

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide;

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C16)

3-(4-chlorophenyl)-4-[4(methylsulfonyl)phenyl]-2(3H)-oxazolone;

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C17)

4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide;

-110-

C18)

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2cyclopenten-1-one;

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C19)

4-(2-methyl-4-phenyl-5oxazolyl)benzenesulfonamide;

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C20)

3-(4-fluorophenyl)-4-[4(methylsulfonyl)phenyl]-2(3H)-oxazolone;

-111-

C21)

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5-(4-fluorophenyl)-1-[4(methylsulfonyl)phenyl]-3-(trifluoromethyl)1H-pyrazole;

C22)

4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

C23)

$$H_2N$$
  $CF_3$ 

4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5yl]benzenesulfonamide;

-112-

C24)

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

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C25)

N-[2-(cyclohexyloxy)-4nitrophenyl]methanesulfonamide;

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C26)

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide;

-113-

C27)

3-(4-chlorophenoxy)-4-

5 [(methylsulfonyl)amino]benzenesulfonamide;

C28)

3-(4-fluorophenoxy)-4-

10 [(methylsulfonyl)amino]benzenesulfonamide;

C29)

3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl) amino]benzenesulfonamide;

PCT/US99/30776

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C30)

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3phenoxy-2(5H)-furanone;

C31)

5

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide;

C32)

3-[(2,4-dichlorophenyl)thio]-4[(methylsulfonyl)amino]benzenesulfonamide;

-115-

C33)

1-fluoro-4-[2-[4-

(methylsulfonyl)phenyl]cyclopenten-1-

yl]benzene;

C34)

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10

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-

pyrazol-1-yl]benzenesulfonamide;

C35)

3-[1-[4-(methylsulfonyl)phenyl]-4(trifluoromethyl)-1H-imidazol-2-yl)pyridine;

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C36)

4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1Himidazol-1-yl]benzenesulfonamide;

-117-

C37)

4-[5-(hydroxymethyl)-3-phenylisoxazol-4yl]benzenesulfonamide;

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C38)

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide;

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C39)

$$H_2N$$
  $CF_2H$ 

4-[5-(difluoromethyl)-3-phenylisoxazol-4yl]benzenesulfonamide;

-118-

C40)

[1,1':2',1"-terphenyl]-4-sulfonamide;

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C41)

4-(methylsulfonyl)-1,1',2],1"-terphenyl;

10 C42)

4-(2-phenyl-3-pyridinyl)benzenesulfonamide;

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C43)

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N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide; and

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C44)

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide;

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-120-

47)

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More preferred COX-2 inhibitors that may be used in the present invention are selected from the group consisting of:

10 C1)

JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)2-fluorobenzenesulfonamide;

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C3)

2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2
cyclopenten-1-one;

10

C4)

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide;

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C5)

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3
phenyl-2(5H)-furanone;

PCT/US99/30776

C6)

4-(5-methyl-3-phenylisoxazol-4yl)benzenesulfonamide;

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C7)

N-[[4-(5-methyl-3-phenylisoxazol4yl]phenyl]sulfonyl]propanamide;

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C8)

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide;

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Still more preferably, the COX-2 inhibitors that may be used in the present invention include, but are not limited to celecoxib, valdecoxib, parecoxib, rofecoxib, and Japan Tobacco JTE-522.

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## Dosage of MMP and COX-2 Inhibitors

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Dosage levels of MMP and COX-2 inhibitors on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 1.0 mg to about 1,000 mg. The amount of active ingredient that may be combined with other anticancer agents to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease being treated and form of administration.

Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from in vitro initially can provide useful guidance on the proper doses for patient administration. Studies in animal models also generally may be used for guidance regarding effective dosages for treatment of cancers in accordance with the present invention. In terms of treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route administered, the condition of the particular patient, etc. Generally speaking, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with

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the concentrations found to be effective in vitro. Thus, where an compound is found to demonstrate in vitro activity at, e.g., 10  $\mu$ M, one will desire to administer an amount of the drug that is effective to provide about a 10  $\mu$ M concentration in vivo. Determination of these parameters are well within the skill of the art.

These considerations, as well as effective formulations and administration procedures are well known in the art and are described in standard textbooks.

## Administration Regimen

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Any effective treatment regimen can be utilized and readily determined and repeated as necessary to effect treatment. In clinical practice, the compositions containing a MMP and COX-2 inhibitor alone or in combination with other therapeutic agents are administered in specific cycles until a response is obtained.

- 20 For patients who initially present without advanced or metastatic cancer, a MMP and COX-2 inhibitor in combination with radiation therapy, is used as a continuous post-treatment therapy in patients at risk for recurrence or metastasis (for example, in adenocarcinoma of the prostate, risk for metastasis is based upon high PSA, high Gleason's score, locally extensive disease, and/or pathological evidence of tumor invasion in the surgical specimen). The goal in these patients is to inhibit the growth of potentially
- 30 metastatic cells from the primary tumor during surgery

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and inhibit the growth of tumor cells from undetectable residual primary tumor.

For patients who initially present with advanced or metastatic cancer, a MMP and COX-2 inhibitor in combination with radiation therapy of the present invention is used as a continuous supplement to, or possible replacement for hormonal ablation. The goal in these patients is to slow or prevent tumor cell growth from both the untreated primary tumor and from the existing metastatic lesions.

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Also included in the combination of the invention are the isomeric forms, prodrugs and tautomers of the described compounds and the pharmaceutically-acceptable salts thereof. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, 15 succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, 20 ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, b-hydroxybutyric, galactaric and galacturonic acids.

Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metal ions. Such salts can be made from the ions of

aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-

dibenzylethylenediamine, chloroprocaine, choline, 5 diethanolamine, ethylenediamine, meglumine (Nmethylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention. 10

A MMP or COX-2 inhibitor of the present invention can be formulated as a pharmaceutical composition. Such a composition can then be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing 15 conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used 20 herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 25 1975. Another discussion of drug formulations can be found in Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York,

Injectable preparations, for example, sterile 30 injectable aqueous or oleaginous suspensions can be

N.Y., 1980.

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formulated according to the known art using suitable dispersing or wetting agents and suspending agents. sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, 5 as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending 10 medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. addition, fatty acids such as oleic acid find use in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, 15 polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Suppositories for rectal administration of the drug

20 can be prepared by mixing the drug with a suitable

nonirritating excipient such as cocoa butter, synthetic

mono- di- or triglycerides, fatty acids and polyethylene

glycols that are solid at ordinary temperatures but

liquid at the rectal temperature and will therefore melt

25 in the rectum and release the drug.

Solid dosage forms for oral administration can include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, a contemplated

aromatic sulfone hydroximate inhibitor compound can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlledrelease formulation as can be provided in a dispersion 10 of active compound in hydroxypropylmethyl cellulose. the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with 15 enteric coatings.

For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. A contemplated MMP or COX-2 inhibitor compound can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

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Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions,

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solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.

The phrase "antineoplastic agents" includes agents 10 that exert antineoplastic effects, i.e., prevent the development, maturation, or spread of neoplastic cells, directly on the tumor cell, e.g., by cytostatic or cytocidal effects, and not indirectly through mechanisms such as biological response modification. There are 15 large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in preclinical development, which could be included in the present invention for treatment of neoplasia by combination drug chemotherapy. For convenience of 20 discussion, antineoplastic agents are classified into the following classes, subtypes and species:

ACE inhibitors, alkylating agents,

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angiogenesis inhibitors,
angiostatin,
anthracyclines/DNA intercalators,
anti-cancer antibiotics or antibiotic-type agents,
antimetabolites,

antimetastatic compounds,
asparaginases,

bisphosphonates, cGMP phosphodiesterase inhibitors, calcium carbonate, cyclooxygenase-2 inhibitors DHA derivatives, 5 DNA topoisomerase, endostatin, epipodophylotoxins, genistein, hormonal anticancer agents, 10 hydrophilic bile acids (URSO), immunomodulators or immunological agents, integrin antagonists interferon antagonists or agents, MMP inhibitors, 15 miscellaneous antineoplastic agents, monoclonal antibodies, nitrosoureas, NSAIDs, ornithine decarboxylase inhibitors, 20 pBATTs, radio/chemo sensitizers/protectors, retinoids selective inhibitors of proliferation and migration 25 of endothelial cells, selenium, stromelysin inhibitors, taxanes, vaccines, and vinca alkaloids. 30

WO 00/37107

The major categories that some preferred antineoplastic agents fall into include antimetabolite agents, alkylating agents, antibiotic-type agents, hormonal anticancer agents, immunological agents, interferon-type agents, and a category of miscellaneous antineoplastic agents. Some antineoplastic agents operate through multiple or unknown mechanisms and can thus be classified into more than one category.

A first family of antineoplastic agents which may be used in combination with the present invention consists of 10 antimetabolite-type antineoplastic agents. Antimetabolites are typically reversible or irreversible enzyme inhibitors, or compounds that otherwise interfere with the replication, translation or transcription of nucleic acids. Suitable antimetabolite antineoplastic agents that 15 may be used in the present invention include, but are not limited to acanthifolic acid, aminothiadiazole, anastrozole, bicalutamide, brequinar sodium, capecitabine, carmofur, Ciba-Geigy CGP-30694, cladribine, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine 20 conjugates, cytarabine ocfosfate, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, finasteride, floxuridine, fludarabine phosphate, N-(2'-furanidyl)-5-fluorouracil, 25 Daiichi Seiyaku FO-152, fluorouracil (5-FU), 5-FUfibrinogen, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, nafarelin, norspermidine, nolvadex, NCI NSC-127716, NCI 30 NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical

PL-AC, stearate; Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, tyrosine protein kinase inhibitors, Taiho UFT, toremifene, and uricytin.

Preferred antimetabolite agents that may be used in the present invention include, but are not limited to, those identified in Table No. 6, below.

Table No. 6. Antimetabolite agents

G		T_*	<del> </del>	
Compound	Common	Company	Reference	Dosage
	Name/		1	
1.3-	Trade Name			
<b>,</b> -	anastrozole	Zeneca	EP 296749	1-mg/day
Benzenediaceto	; ARIMIDEX®		1	
nitrile, alpha,	ļ			
alpha,alpha',a lpha'-				
tetramethyl-5-				
(1H-1,2,4-				
triazol-1-ylme				
thyl)-				
Propanamide,	bicalutamid	Zeneca	EP 100172	50 mg once
N-[4-cyano-3-	e; CASODEX®			daily
(trifluorometh			1	,
yl)phenyl]-3-	:			
[(4-		•		
fluorophenyl)				
sulfonyl]-2-				
hydroxy-2-				
methyl-, (+/-				
) –				
	capecitabin	Roche	US 5472949	
	е			
Adenosine, 2-	cladribine;	Johnson &	EP 173059	0.09
chloro-2'-	2-CdA;	Johnson		mg/kg/day
deoxy-; 2-	LEUSTAT;			for 7
chloro-2'-	LEUSTA-			days.
deoxy-(beta)-	TIN®;			
D-adenosine)	LEUSTA-TIN®			
	in-jection;			
	LEUSTATINE®			
	; RWJ-			

Compound	Common.	Company	Reference	Dosage
Jonepoul	Name/	Jen Per J		Lobugo
	Trade Name			
	26251;			
2(1H)-	cytarabine	Yamasa	EP 239015	100 - 300
Pyrimidinone,	ocfosfate;	Corp	111 235013	mg/day for
4-amino-1-[5-	ara CMP	COLD		2 weeks
0-	Į.			2 weeks
~	stearyl			
[hydroxy(octad	ester; C-			
ecyloxy)phosph	18-PCA;			
inyl]-beta-D-	cytarabine			
arabinofuranos	phosphate			
yl]-,	stearate;			
monosodium	Starasid;			
salt	YNK-O1;			
	CYTOSAR-U®			
4-Azaandrost-	finasteride	Merck &	EP 155096	
1-ene-17-	; PROPECIA®	Co		:
carboxamide,				
N-(1,1-				
dimethylethyl)				
-3-oxo- ,				
(5alpha,17beta				
)				
	fluorouraci		US 4336381	
	1 (5-FU)			
Fludarabine	fludarabine	Southern	US 4357324	25 / /
phosphate.	phosphate;	Research		25 mg/m /d
9H-Purin-6-	2-F-araAMP;	Institute		IV over a
amine, 2-	Fludara;	; Berlex		period of
fluoro-9-(5-0-	Fludara iv;			approx-
phosphono-	Fludara			imately 30
beta- D-	Oral; NSC-			minutes
arabinofuranos	312887; SH-			daily for
yl)	573; SH-			5 con-
· · · ·	584; SH-			secutive
	586;			days,
	300,			commenced
				every 28
				days.
	gemcitabi ne	Eli Lily	US 4526988	
N-(4-(((2,4-	methotrexat	Hyal	US 2512572	tropho-
diamino- 6-	e iv, Hyal;	Pharma-		blastic
pteridinyl)met	HA +	ceutical;		diseases:
hyl)methylamin	methotrexat	American		15 to 30
o)benzoyl)-L-		Home		i i
O)DettroAT)-P-	e, Hyal;	LHOME		mg/d

WO 00/37107

Compound	Common	Сотралу	Reference	Dosage
_	Name/			_
	Trade Name			
glutamic acid	methotrexat	Products;		orally or
	e iv, HIT	Lederle		intra-
·	Technolog;			muscularly
				in a five-
				day course
·				(repeated
		÷. •		3 to 5
			X 2	times as
				needed)
Luteinizing	nafarelin	Roche	EP 21234	
hormone-				
releasing		•		
factor (pig),				
6-[3-(2-				
naphthalenyl)-				
D-alanine]-			2002505	
	pentostatin	Warner-	JS 3923785	
	; CI-825; DCF;	Lambert		
	deoxycoform			
	ycin;			
	Nipent;			
	NSC-218321;		1	
	Oncopent;			
Ethanamine, 2-	toremifene;	Orion	EP 95875	60 mg/d
[4-(4-chloro-	FARESTON®	Pharma		
1,2-diphenyl-				
1-				
butenyl)phenox				
y]-N,N-	·			
dimethyl-,				
(Z)-				

A second family of antineoplastic agents which may be used in combination with the present invention consists of alkylating-type antineoplastic agents. The alkylating agents are believed to act by alkylating and cross-linking guanine and possibly other bases in DNA, arresting cell division. Typical alkylating agents include nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin, and various nitrosoureas. A

disadvantage with these compounds is that they not only attack malignant cells, but also other cells which are naturally dividing, such as those of bone marrow, skin, gastro-intestinal mucosa, and fetal tissue. Suitable alkylating-type antineoplastic agents that may be used. in the present invention include, but are not limited to, Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine (BiCNU), Chinoin-139, Chinoin-153, 10 chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, dacarbazine, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, 15 elmustine, Erbamont FCE-24517, estramustine phosphate sodium, etoposide phosphate, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, mycophenolate, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, 20 oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, thiotepa, Yakult Honsha SN-22, spiromus-tine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone,

Preferred alkylating agents that may be used in the present invention include, but are not limited to, those identified in Table No. 7, below.

30 Table No. 7. Alkylating agents

tetraplatin and trimelamol.

	Common	Company	Reference	Dosage
Compound	Common Name/Trade	Company	Reference	Dosage
	Name/Trace			
Disting		Johnson	US 4657927.	360 mg/m(
Platinum,	carboplatin;	_	US 4140707.	squared)
diammine[1,1	PARAPLATIN ®	Matthey	05 4140/0/.	I.V. on
-cyclobu-				1
tanedicarbox				day 1
ylato(2-)]-,				every 4
(SP-4-2)-				weeks.
Carmustine,	BiCNU®	Ben Venue	1 -	Preferred:
1,3-bis (2-		Labora-	253 (11):	150 to 200
chloroethyl)		tories,	1590-1592.	mg/m <sup>2</sup>
-1-nitro-		Inc.		every 6
sourea				wks.
	etoposide	Bristol-	US 4564675	
	phosphate	Myers	05 1301073	
	phosphace	Squibb		ļ
	thiotepa	bquibb		
Platinum,	cisplatin;	Bristol-	US 4177263	
diamminedi-	PLATINOL-AQ	Myers	0.5 12	
chloro-,	THATHOU IN	Squibb		
(SP-4-2)-		Dquino		
dacarbazine	DTIC Dome	Bayer		2 to
Cacarrazine	DITC DAME	Layer	ł	4.5mg/kg/d
				ay for 10
		-		days;
				250mg/
		,		square
				meter body
				surface/
				day I.V.
				for 5 days
	·			every 3
				weeks
ifosfamide	IFEX	Bristol-		4-5 g/m
Trostamide	11457	Meyers		(square)
		Squibb		single
		STATIO		bolus
				dose, or
<u> </u>				1.2-2 g/m
				į.
				(square) I.V. over
				1
		<del> </del>	US 4537883	5 days.
	cyclophosph amide		US 453/003	
cis-	Platinol	Bristol-		20 mg/M <sup>2</sup>

Compound	Common Name/Trade Name	Company	Reference	Dosage
diaminedichl oroplatinum	Cisplatin	Myers Squibb		IV daily for a 5 day cycle.

A third family of antineoplastic agents which may be used in combination with the present invention consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents that may be used in the present invention include, but are not limited to Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, 10 bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-15 88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, 20 Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-25 5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone,

SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313,

15

Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindamycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

Preferred antibiotic anticancer agents that may be used in the present invention include, but are not limited to, those agents identified in Table No. 8, below.

Table No. 8. Antibiotic anticancer agents

Compound	Common Name/ Trade Name	Company	Reference	Dosage
4-Hexenoic acid, 6-(1,3- dihydro-4- hydroxy-6- methoxy-7- methyl-3-oxo-5- isobenzofuranyl )-4-methyl-, 2- (4- morpholinyl)eth yl ester, (E)-	mycopheno- late mofetil	Roche	WO 91/19498	1 to 3 gm/d
	mitoxan- trone		US 4310666	
	doxorubicin		US 3590028	
Mitomycin and/or mitomycin-C	Mutamycin	Bristol- Myers Squibb Oncology/ Immun- ology		After full hemato- logical recovery from any previous

Compound	Common Name/ Trade Name	Company	Reference	Dosage
				chemo-
				therapy:
				20 mg/m <sup>2</sup>
				intra-
				venously
				as a
				single
				dose via
				a
				function-
				ing
				intra-
1				venous
				catheter.

A fourth family of antineoplastic agents which may be used in combination with the present invention consists of synthetic nucleosides. Several synthetic nucleosides have been identified that exhibit anticancer activity. A well known nucleoside derivative with strong anticancer activity is 5-fluorouracil (5-FU). 5-Fluorouracil has been used clinically in the treatment of malignant tumors, including, for example, carcinomas, sarcomas, skin cancer, cancer of the digestive organs, 10 and breast cancer. 5-Fluorouracil, however, causes serious adverse reactions such as nausea, alopecia, diarrhea, stomatitis, leukocytic thrombocytopenia, anorexia, pigmentation, and edema. Derivatives of 5fluorouracil with anti-cancer activity have been 15 described in U.S. Pat. No. 4,336,381. Further 5-FU derivatives have been described in the following patents listed in Table No. 9, hereby individually incorporated by reference herein.

Table No. 9. 5-Fu derivatives

JP 50-50383	JP 50-50384	JP 50-64281
L		

	JP 51-146482	JP 53-84981	
ı		L	11

U.S. Pat. No. 4,000,137 discloses that the peroxidate oxidation product of inosine, adenosine, or cytidine with methanol or ethanol has activity against

- lymphocytic leukemia. Cytosine arabinoside (also referred to as Cytarabin, araC, and Cytosar) is a nucleoside analog of deoxycytidine that was first synthesized in 1950 and introduced into clinical medicine in 1963. It is currently an important drug in
- the treatment of acute myeloid leukemia. It is also active against acute lymphocytic leukemia, and to a lesser extent, is useful in chronic myelocytic leukemia and non-Hodgkin's lymphoma. The primary action of araC is inhibition of nuclear DNA synthesis. Handschumacher,
- 15 R. and Cheng, Y., "Purine and Pyrimidine
  Antimetabolites", Cancer Medicine, Chapter XV-1, 3rd
  Edition, Edited by J. Holland, et al., Lea and Febigol,
  publishers.

5-Azacytidine is a cytidine analog that is primarily used in the treatment of acute myelocytic leukemia and myelodysplastic syndrome.

2-Fluoroadenosine-5'-phosphate (Fludara, also referred to as FaraA) is one of the most active agents in the treatment of chronic lymphocytic leukemia. The compound acts by inhibiting DNA synthesis. Treatment of cells with F-araA is associated with the accumulation of cells at the G1/S phase boundary and in S phase; thus, it is a cell cycle S phase-specific drug. InCorp of the active metabolite, F-araATP, retards DNA chain elongation. F-araA is also a potent inhibitor of

-141-

ribonucleotide reductase, the key enzyme responsible for the formation of dATP. 2-Chlorodeoxyadenosine is useful in the treatment of low grade B-cell neoplasms such as chronic lymphocytic leukemia, non-Hodgkins' lymphoma, and hairy-cell leukemia. The spectrum of activity is similar to that of Fludara. The compound inhibits DNA synthesis in growing cells and inhibits DNA repair in resting cells.

5

A fifth family of antineoplastic agents which may be used in combination with the present invention 10 consists of hormonal agents. Suitable hormonal-type antineoplastic agents that may be used in the present invention include, but are not limited to Abarelix; Abbott A-84861; Abiraterone acetate; Aminoglutethimide; 15 anastrozole; Asta Medica AN-207; Antide; Chugai AG-041R; Avorelin; aseranox; Sensus B2036-PEG; Bicalutamide; buserelin; BTG CB-7598; BTG CB-7630; Casodex; cetrolix; clastroban; clodronate disodium; Cosudex; Rotta Research CR-1505; cytadren; crinone; deslorelin; droloxifene; dutasteride; Elimina; Laval University EM-800; Laval 20 University EM-652; epitiostanol; epristeride; Mediolanum EP-23904; EntreMed 2-ME; exemestane; fadrozole; finasteride; flutamide; formestane; Pharmacia & Upjohn FCE-24304; ganirelix; goserelin; Shire gonadorelin 25 agonist; Glaxo Wellcome GW-5638; Hoechst Marion Roussel Hoe-766; NCI hCG; idoxifene; isocordoin; Zeneca ICI-182780; Zeneca ICI-118630; Tulane University J015X; Schering Ag J96; ketanserin; lanreotide; Milkhaus LDI-200; letrozol; leuprolide; leuprorelin; liarozole; lisuride hydrogen maleate; loxiglumide; mepitiostane; Leuprorelin; Ligand 30 Pharmaceuticals LG-1127; LG-1447; LG-2293; LG-2527; LG-

2716; Bone Care International LR-103; Lilly LY-326315; Lilly LY-353381-HCl; Lilly LY-326391; Lilly LY-353381; Lilly LY-357489; miproxifene phosphate; Orion Pharma MPV-2213ad; Tulane University MZ-4-71; nafarelin; nilutamide; Snow Brand NKS01; octreotide; Azko Nobel ORG-31710; Azko Nobel ORG-31806; orimeten; orimetene; orimetine; ormeloxifene; osaterone; Smithkline Beecham SKB-105657; Tokyo University OSW-1; Peptech PTL-03001; Pharmacia & Upjohn PNU-156765; quinagolide; ramorelix; Raloxifene; 10 statin; sandostatin LAR; Shionogi S-10364; Novartis SMT-487; somavert; somatostatin; tamoxifen; tamoxifen methiodide; teverelix; toremifene; triptorelin; TT-232; vapreotide; vorozole; Yamanouchi YM-116; Yamanouchi YM-511; Yamanouchi YM-55208; Yamanouchi YM-53789; Schering 15 AG ZK-1911703; Schering AG ZK-230211; and Zeneca ZD-182780.

Preferred hormonal agents that may be used in the present invention include, but are not limited to, those identified in Table No. 10, below.

20

Table No. 10. Hormonal agents

Compound	Common Name/ Trade Name	Company	Reference	Dosage
2-	EntreMed;	EntreMe		
methoxyestradiol	2-ME	d		
N-(S)- tetrahydrofuroyl -Gly-D2Nal- D4ClPhe-D3Pal- Ser-NMeTyr- DLys(Nic)-Leu- Lys(Isp )-Pro- DAla-NH2	A-84861	Abbott		
	raloxi-			

	Γ	Τ	T	<del> </del>
Compound	Common	Company	Reference	Dosage
	Name/	1		
	Trade			
	Name			
	fene			
[3R-1-(2,2-	AG-041R	Chugai	WO 94/19322	
Dimethoxyethyl)-				
3-((4-		l		
methylphenyl)ami				
nocarbonylmethyl				
)-3-(N'-(4-me			ļ	
thylphenyl)ureid				
o)-indoline-2-		l	1	
one]				
	AN-207	Asta	WO 97/19954	
		Medica		
Ethanamine, 2-	toremif-	Orion	EP 95875	60 mg/d
[4-(4-chloro-	ene;	Pharma		J.
1,2-diphenyl-1-	FARESTON®			
butenyl)phenoxy]		}		
-N, N-dimethyl-,		ļ		
(Z) ~		}		
Ethanamine, 2-	tamoxifen	Zeneca	US 4536516	For
[4-(1,2-	NOLVADEX (	1		patients
diphenyl-1-	R)			with
butenyl)phenoxy]				breast
-N, N-dimethyl-,				cancer,
(Z)-				the
				recommende
				d daily
				dose is
				20-40 mg.
				Dosages
				greater
				than 20 mg
				per day
				should be
				divided
				(morning
				and
				evening).
D-Alaninamide N-	Antide;	Ares-	WO 89/01944	25 or
acetyl-3-(2-	ORF-23541	Serono	05/01544	50microg/
naphthalenyl)-D-				kg sc
alanyl-4-chloro-				ng ac
D-phenylalanyl-				
3-(3 -				
L <del>~_\~</del>	L	l	L	

	r	Γ.		
Compound	Common	Company	Reference	Dosage
	Name/			
	Trade			
	Name			
pyridinyl)-D-				
alanyl-L-seryl-				ļ
N6-(3-				
pyridinylcarbony				
1)L-lysyl-N6-				
(3-pyridinylca				}
rbonyl)-D-lysyl-	•			
L-leucyl-N6-(1-				
methylethyl)-L-				
lysyl-L-prolyl-		:		
	B2036-	Sensus		
	PEG;			
	Somaver;			
	Trovert			
4-Methyl-2-[4-	EM-800;	Laval		
[2-(1-	EM-652	Univers		
piperidinyl)etho		ity		
xy]phenyl]-7-		· -		
(pivaloyloxy)-3-		ļ		
[4-(pivaloylox				
y)phenyl]-2H-1-		ļ		
benzopyran				
	letrozol		US 4749346	
	goserelin		US 4100274	
3-[4-[1,2-	GW-5638	Glaxo		
Diphenyl-1(Z)-		Wellcom		
butenyl]phenyl]-		e		
2(E)-propenoic				
acid				
Estra-1,3,5(10)-	ICI-	Zeneca	EP 34/6014	250mg/mth
triene-3,17-	182780;			
diol, 7-[9-	Faslodex;			
[(4,4,5,5,5-	ZD-182780			
pentafluoro-				
pentyl)				
sulfinyl]-				
nonyl]-,				
(7alpha,17beta)-				
	J015X	Tulane		
		Univers		i
		ity		
	LG-1127;	Ligand		
	LG-1447	Pharmac		

Compound	Common	Company	Reference	Dosage
COMPOUNT	Name/	COMPANY	vererere	Dosage
	Trade			
	Name			
		eutical		
		s		
***************************************	LG-2293	Ligand		
	10-2273	Pharmac		
		eutical		
		S		
	LG-2527;	Ligand		
	LG-2716	Pharmac		
	20 2720	eutical		
		s		
	buser-	Peptech		
	elin,			
	Peptech;			
	des-			
	lorelin,	[		
	Peptech;			
	PTL-			
	03001;			
	trip-			ł
	torelin,			
	Peptech	<u> </u>		
	LR-103	Bone		
		Care		
		Interna		
		tional		
[2-(4-	LY-326315	Lilly	WO 9609039	
Hydroxyphenyl)-				
6-				
hydroxynaphthale				
n-1-yl] [4-[2-				
(1-				
piperdinyl)ethox				
y]pheny				
l]methane				
hydrochloride	TV	T 4 1 1		
	LY-	Lilly		
	353381- HCl			
	LY-326391	т;13		
	LY-353381	Lilly		
	LY-353381 LY-357489	Lilly		
<u> </u>	MPV-	Lilly	ED 476044	0 3-300
		Orion	EP 476944	0.3-300 mg
L	2213ad	Pharma	<u> </u>	L

Compound	Common.	Company	Reference	Dosage
,	Name/			
	Trade			
	Name			
Isobutyryl-Tyr-	MZ-4-71	Tulane		
D-Arg-Asp-Ala-		Univers	i	
Ile-(4-Cl)-Phe-		ity		
Thr-Asn-Ser-Tyr-				
Arg-Lys-Val-Leu-				
(2-				
aminobutyryl)-				
Gln-Leu-Ser-Ala-				
Arg-Lys-Leu-Leu-				
Gln-Asp-Ile-Nle-				
Ser 4-				
guanidinobu				
tylamide				
Androst-4-ene-	NKS01;	Snow	EP 300062	
3,6,17-trione,	14alpha-	Brand		
14-hydroxy-	OHAT;			
	140HAT			
3beta,16beta,17a	OSW-1			
lpha-				
trihydroxycholes				
t-5-en-22-one-		1		
16-0-(2-0-4-				
methoxybenzoyl-				
beta-D-xy				
lopyranosyl)-(1-				
3) (2-0-acetyl-				
alpha-L-				
arabinopyranosid				
e)		l		
Spiro[estra-4,9-	Org-	Akzo	EP 289073	
diene-	31710;	Nobel		
17,2'(3'H)-	Org-31806			
furan]-3-one,				
11-[4-				
(dimethylamino)p				
henyl] -4',5'-				
dihydro-6-				
methyl-,				
(6beta, 11beta, 17				
beta)-				<del> </del>
(22RS)-N-(1,1,1-	PNU-	Pharmac		
trifluoro-2-	156765;	ia &		
phenylprop-2-	FCE-28260	Upjohn		l

		T =	1 = 2	·
Compound	Common	Company	Reference	Dosage
	Name/			
	Trade			
	Name			
y1)-3-oxo-4-aza-				
5alpha-androst-				
1-ene-17beta -				
carboxamide				
1-[(benzofuran-		Menarin		
2y1)-4-		li .		
chlorophenylmeth				
yl]imidazole				
Tryptamine		Rhone-	WO 96/35686	
derivatives		Poulenc	1 10 30/33000	
		Rorer	·	
Permanenting		Pharmos	NO 05 /26720	
Permanently ionic		PHALINOS	WO 95/26720	·
1				
derivatives of steroid	1			
hormones and	1	1		
their				
antagonists				
Novel		Meiji	WO 97/30040	
tetrahydronaph		Seika		
thofuranone				
derivatives				
	SMT-487;	Novarti		
	90Y-	s		
	octreo-	1		
	tide			
D-Phe-Cys-Tyr-D-	TT-232			
Trp-Lys-Cys-Thr-				
NH2				
2-(1H-imidazol-	YM-116	Yamanou		
4-ylmethyl)-9H-		-chi		
carbazole				
monohydrochlorid				
e monohydrate				
4-[N-(4-	YM-511	Yamanou		
bromobenzyl)-N-		-chi		
(4-				
cyanophenyl)amin				
o]-4H-1,2,4-		İ		
triazole				
	30/ EE000	77		
2-(1H-imidazol-	YM-55208;	Yamanou	<u> </u>	

	<del> </del>		·	
Compound	Common.	Company	Reference	Dosage
	Name/			
	Trade			
	Name			
4-ylmethyl)-9H-	YM-53789	-chi		İ
carbazole				
monohydrochlorid				
e monohydrate				
	ZK-	Scherin		
	1911703	g AG		
	ZK-230211	Scherin		
		g AG		
	abarelix	Praecis		
		Pharmac		
		eutical		
		s	:	
Androsta-5,16-	abira-	BTG		
dien-3-ol, 17-	terone			
(3-pyridinyl)-,	acetate;			
acetate (ester),	CB-7598;	<del>!</del>		
(3beta)-	CB-7630			
2,6-	aminoglut	Novarti	US 3944671	
Piperidinedione,	ethimide;	s		
3-(4-	Ciba-			
aminophenyl)-3-	16038;			
ethyl-	Cytadren;			
_	Elimina;			
ļ	Orimeten;			
	Orimet-			
	ene;			
	Orimetine			
1,3-	anastro-	Zeneca	EP 296749	1mg/day
Benzenediacetoni	zole;			
trile,alpha,alph	Arimidex;			
a,alpha',alpha'-	ICI-			
tetramethyl-5-	D1033;			
(1H-1,2,4-	ZD-1033			
triazol-1-ylme				
thyl)-				
5-0xo-L-prolyl-	avorelin;	Medi-	EP 23904	
L-histidyl-L-	Meterelin	olanum		
tryptophyl-L-				
seryl-L-tyrosyl-				
2-methyl-D-				
tryptophyl- L-				
leucyl-L-				1
arginyl-N-ethyl-				

Compound	Common Name/	Company	Reference	Dosage
	Trade			
	Name			
L-prolinamide				
Propanamide, N-	bicalutam	Zeneca	EP 100172	
[4-cyano-3-	ide;			
(trifluoromethyl	Casodex;			
)pheny1]-3-[(4-	Cosudex;	İ		
fluorophenyl)	ICI-			
sulfonyl]-2-	176334			
hydroxy-2-				·
methyl-, (+/-)-				
Luteinizing	busere-	Hoechst	GB	200-600
hormone-	lin; Hoe-	Marion	15/23623	microg/day
releasing factor	766;	Roussel		
(pig), 6-[O-	Profact;			
(1,1-	Receptal;			
dimethylethyl)-	s-746766;			
D-serine] -9-(N-	Suprecor;	}		
ethyl-L-	Suprecur;			
prolinamide)-10-	Supre-			
deglycinamide-	fact;			
	Suprefakt			
D-Alaninamide,	cetro-	Asta	EP 29/9402	
N-acetyl-3-(2-	relix;	Medica		
naphthalenyl)-D-	SB-075;			
alanyl-4-chloro-	SB-75			
D- phenylalanyl-				
3-(3-pyridinyl)-				
D-alanyl-L-				
seryl-L-tyrosyl-		1		
N5-				
(aminocarbonyl)-	1			
D-ol-L-leucyl-L-	ļ			
arginyl-L-		1	,	
prolyl-	clodro-	Scherin		-
Phosphonic acid,	nate	g AG		
(dichloromethyle	disodium,	la vo		
ne)bis-, disodium salt-	Leiras;			
disoutum sait-	Bonefos;			
	Clasto-			
1	ban; KCO-			
1				
	1			
Luteinizing	692 deslore-	Roberts	US 4034082	

	<u> </u>	Company	Reference	Dosage
Compound	Common	Company	Kererence	Dosage
	Name/ Trade			
	Name			
releasing factor	gonado-	·		
(pig), 6-D-	relin	ļ		
tryptophan-9-(N-	analogue,			
ethyl-L-	Roberts;	-		1
prolinamide)-10-	LHRH			
deglycinamide-	analogue,			
	Roberts;			
	Somagard		TD 54160	
Phenol, 3-[1-[4-	droloxi-	Klinge	EP 54168	
[2-	fene; FK-			
(dimethylamino)e	435; K-			
thoxy]phenyl]-2-	060; K-			
phenyl-1-	21060E;			
butenyl]-, (E)-	RP 60850			
[CA S]		-7	<del> </del>	
4-Azaandrost-1-	dutaster-	Glaxo		
ene-17-	ide; GG-	Wellcom		
carboxamide, N-	745; GI-	e		
(2,5-	198745			
bis(trifluoromet				
hyl)phenyl)-3-				
oxo-, (				ļ
5alpha, 17beta) -		M-:	770 2220215	<del> </del>
Androstan-17-ol,	epitio-	Shionog	US 3230215	
2,3-epithio-,	stanol;	ļi		1
(2alpha, 3alpha, 5	10275-S;			
alpha,17beta)-	epithioan	1	1	
	drostan-			
	ol; S-			
	10275;			
	Thiobres-			
	tin;			
2 2 . 2	Thiodrol	0-3-1-	ED 200227	0.4-
Androsta-3,5-	epriste-	Smith-	EP 289327	160mg/day
diene-3-	ride;	Kline		Toning/day
carboxylic acid,	ONO-9302;	Beecham		
17-(((1,1-	SK&F-			
dimethylethyl)am	3			
ino)carbonyl)-	SKB-			
(17beta) -	105657	<del> </del>		<del>                                     </del>
estrone 3-0-	estrone			
sulfamate	3-0-			
	sulfamate	<u></u>		

				I
Compound	Common	Company	Reference	Dosage
	Name/			
	Trade			
	Name			
19-Norpregna-	ethinyl	Scherin	DE 1949095	
1,3,5(10)-trien-	estradiol	g AG		
20-yne-3,17-	sulfon-			
diol, 3-(2-	ate; J96;			
propanesulfonate	Turister-			
) , (17alpha)-	on			
Androsta-1,4-	exemes-	Pharmac	DE 3622841	5mg/kg
diene-3,17-	tane;	ia &		
dione, 6-	FCE-24304	Upjohn		
methylene-	,	-23		
Benzonitrile, 4-	fadrozo-	Novarti	EP 165904	1 mg po
(5,6,7,8-	le;	s		bid
tetrahydroimidaz	Afema;	~		224
o[1,5-a]pyridin-	Arensin;	ŀ		
5-y1)-,	CGS-	1		
monohydrochlorid	16949;			
e	CGS-			
	16949A;			
	CGS-			
	20287;			
	fadrozole	-		
	monohydro			
	chloride	1		
4-Azaandrost-1-	finaster-	Merck &	EP 155096	5mg/day
ene-17-	ide;	Co	1 133030	Jang, Cary
carboxamide, N-	Andozac;			
(1,1-	ChibroPro			
dimethylethyl)-	scar;			
3-oxo-,	Finastid;			
(5alpha, 17beta) -	MK-0906;			
(Suipin, 17beu)	MK-906;			
	Procure;			
	Prodel;			
	Propecia;			
	Proscar;			
	Proskar;			
	Prostide;			
	YM-152			
Propanamide, 2-	flutamide	Scherin	US 4329364	
			05 4527304	
methyl-N-[4- nitro-3-	Drogent 1	g		
İ	Drogenil;	Plough		
(trifluoromethyl	Euflex;			
)phenyl]-	Eulexin;	<u> </u>	<u> </u>	<u> </u>

Common	Company	Reference	Dosage
	- Canadana	1020203	Lobuge
· ·			
Name	İ		
Eulexine;			
Flucinom;			
Flutamida			
;			
Fugerel;			
NK-601;			]
Odyne;			
Prostogen	i		
•	ļ		
formest-	Novarti	EP 346953	250 or
i -	s		600mg/day
· -			po
i i			
•		ĺ	
i e	ļ		
1			
I	1		
	Pocho	ED 312052	ļ
1 -	Roche	EP 312032	
1			
	Shire		
lin			
agonist,			
Shire			
goserel-	Zeneca	US 4100274	
in; ICI-			
118630;			
LA.			
ļ		[	
hCG.	Milkhau		
_			
human	NIH		
	Eulexine; Flucinom; Flucinom; Flutamida; Fugerel; NK-601; Odyne; Prostogen at; Sch- 13521 formest- ane; 4- HAD; 4- OHA; CGP- 32349; CRC- 82/01; Depot; Lentaron ganirel- ix; Org- 37462; RS-26306 gonadore- lin agonist, Shire goserel- in; ICI- 118630; Zoladex; Zoladex LA  hCG; gonadotro phin; LDI-200	Name/ Trade Name  Eulexine; Flucinom; Flutamida; Fugerel; NK-601; Odyne; Prostogen at; Sch- 13521  formest- ane; 4- HAD; 4- OHA; CGP- 32349; CRC- 82/01; Depot; Lentaron ganirel- ix; Org- 37462; RS-26306 gonadore- lin agonist, Shire goserel- in; ICI- 118630; Zoladex; Zoladex; Zoladex LA  hCG; gonadoro phin; LDI-200  Milkhau s	Name/ Trade Name  Eulexine; Flucinom; Flutamida; Fugerel; NK-601; Cdyne; Prostogen at; Sch- 13521  formest- ane; 4- HAD; 4- OHA; CGP- 32349; CRC- 82/01; Depot; Lentaron ganirel- ix; Org- 37462; RS-26306 gonadore- lin agonist, Shire goserel- in; ICI- 118630; Zoladex; Zoladex LA  hCG; Milkhau gonadotro phin; LDI-200  Milkhau s HCG; Milk

Compound	Common	Company	Reference	Dosage
Canpoun	Name/	Congany	Verererce	Dosage
	Trade			
:	Name			
	chorionic	<del> </del>	<u> </u>	
	gonadotro			}
	_			
D1232	phin; hCG	DMC	TT 00000	
Pyrrolidine, 1-	idoxifene	BTG	EP 260066	
[2-[4-[1-(4-	; CB-			
iodophenyl)-2-	7386; CB-			
phenyl-1-	7432; SB-			
butenyl]phenoxy]	223030			
et hyl]-, (E)-				ļ
	isocord-	Indena		
0 1/42- 2	oin	<del> </del>		
2,4(1H,3H)-	ketanse-	Johnson	EP 13612	
Quinazolinedione	rin;	&		
, 3-[2-[4-(4-	Aseranox;	Johnson		
fluorobenzoyl)-	Ketensin;	ļ		
1-	KJK-945;			
piperidinyl]ethy	ketanse-			
1]-	rine;			
	Perketan;	i		
	R-41468;			
	Serefrex;	!		
	Serepr-			
	ess;	Ì		
	Sufrexal;			
	Taseron			
L-Threoninamide,	lanreot-	Beaufou	EP 215171	
3-(2-	ide;	r-Ipsen	1	
naphthalenyl)-D-	Angiopept			
alanyl-L-	in; BIM-			
cysteinyl-L-	23014;			ļ
tyrosyl-D-	Dermopept	ŀ		
tryptophyl-L-	in;	İ	•	
lysyl-L-valyl-L-	Ipstyl;	}		
cysteinyl-,	Somatul-		[	
cyclic (2-7)-	ine;			
disulfide	Somatul-			
	ine LP			
Benzonitrile,	letroz-	Novarti	EP 236940	2.5mg/day
4,4'-(1H-1,2,4-	ole; CGS-	s		
triazol-1-	20267;		1	
ylmethylene)bis-	Femara			
Luteinizing	leuprol-	Atrix		
hormone-	ide,			

Compound	Common.	Company	Reference	Dosage
•	Name/			
	Trade			
	Name			
releasing factor	Atrigel;			
(pig), 6-D-	leuprol-			
leucine-9-(N-	ide,			
ethyl-L-	Atrix		٠.	-
prolinamid e)-				
10-				
deglycinamide-				
Luteinizing	leupror-	Abbott	US 4005063	3.75microg
hormone-	elin;		•	sc q 28
releasing factor	Abbott-			days
(pig), 6-D-	43818;			
leucine-9-(N-	Carcinil;			
ethyl-L-	Enantone;			
prolinamide) -10-	Leuplin;			
deglycinamide-	Lucrin;			
	Lupron;			
	Lupron			
	Depot;	1	ļ	
	leuprol-			
	ide,			
	Abbott;			
	leuprol-			
	ide,			
	Takeda;			
	leupror-	1		
	elin,			
	Takeda;			
	Procren			
	Depot;			
	Procrin;			
	Prostap;			
	Prostap			
	SR; TAP-			
	144-SR			
Luteinizing	leupror-	Alza		
hormone-	elin,			
releasing factor	DUROS;			
(pig), 6-D-	leuprolid			
leucine-9-(N-	e, DUROS;			
ethyl-L-	leupror-			
prolinamid e)-	elin			
10-				
deglycinamide-				

Compound	G	T. G	125	15
Compound	Common Name/	Company	Reference	Dosage
	Trade			
111	Name	7-1	TD 060744	200 111
1H-	liaro-	Johnson	EP 260744	300mg bid
Benzimidazole,	zole;	&		
5-[(3-	Liazal;	Johnson		
chlorophenyl)-	Liazol;			
1H-imidazol-1-	liaro-	ľ		ĺ
ylmethyl]-	zole			
	fumarate;			ļ
	R-75251;			
	R-85246;			
Then MI	Ro-85264			
Urea, N'-	lisuride	VUFB	1	
[(8alpha)-9,10-	hydrogen			
didehydro-6-	maleate;			
methylergolin-8-	Cuvalit;			
yl]-N,N-diethyl- , (Z)-2-	Dopergin;		]	
butenedioate	Dopergine			
(1:1)	; Eunal;			
(1.1)	Lysenyl;			
	Lysenyl Forte;			
	Revanil			
Pentanoic acid,	loxiglumi	Rotta	WO 87/03869	
4-[(3,4-	de; CR-	Researc	WO 87703809	
dichlorobenzoyl)	1505	h	ļ	
amino]-5-[(3-	1303	''		
methoxypropyl)				
pentylamino]-5-	İ			
oxo-, (+/-)-				
Androstane, 2,3-	mepitiost	Shionog	US 3567713	
epithio-17-[(1-	ane; S-	i	05 3507713	
methoxycyclopent	10364;	-		
yl)oxy]-,	Thioderon			
(2alpha,3alpha,5				
alpha, 17beta) -		ļ		
Phenol, 4-[1-[4-	miproxife	Taiho	WO 87/07609	20mg/day
[2-	ne		37, 07003	zong/aay
(dimethylamino)e	phosphate			
thoxy]phenyl]-2-	; DP-TAT-			
[4-(1-	59; TAT-			
methylethyl)	59			
phenyl]-1-				
butenyl]-,				
dihydrogen				
7		L		

			D-F	Doggo
Compound	Common	Company	Reference	Dosage
	Name/ Trade			
	Name			
	Natile			
phosphate (ester), (E)-				
	nafarelin	Roche	EP 21/234	
Luteinizing	; NAG,	Roche	EP 21/234	
hormone- releasing factor				
(pig), 6-[3-(2-	Syntex; Nasanyl;			
naphthalenyl)-D-	RS-94991;			
alanine]-	RS-94991-			
aramie)-	298;			
	Synarel;			
	Synarela;			
	Synrelina			
2,4-	nilutam-	Hoechst	US 4472382	
Imidazolidinedio	ide;	Marion	05 11,2502	
ne, 5,5-	Anandron;	Roussel		
dimethyl-3-[4-	Niland-			
nitro-3-	ron;			
(trifluoromethyl	Notost-			
)phenyl]-	ran; RU-			
	23908			
	obesity	Lilly	WO 96/24670	
	gene;			
	diabetes			
	gene;			
	leptin			
L-Cysteinamide,	octreot-	Novarti	EP 29/579	
D-phenylalanyl-	ide;	s		
L-cysteinyl-L-	Longast-			
phenylalanyl-D-	atina;			
tryptophyl-L-	octreot-			
lysyl-L-	ide			
threonyl-N-[2-	pamoate;			
hydroxy-1-	Sandost-			
(hydroxymethyl)p	atin;			
ropyl]-, cyclic	Sandostat			
(2-7)-	in LAR;			
disulfide, [R-	Sandost-			
(R*,R*)]-	atina;			
	Sandost-			
	atine; SMS-201-			
	995			1
Pyrrolidine, 1-	ormelox-	Central	DE 2329201	<del></del>
LATTOTIQUE, I-	Lornerox-	Lentrar	NE 727370T	

Compound	Common	Co	Tn. 5	
Compound	Name/	Company	Reference	Dosage
	Trade	ĺ		
	Name			
[2-(p-(7-	ifene;	Drug		
methoxy-2,2-	6720-	Researc		
dimethyl-3-	CDRI;	h Inst.		
phenyl-4-	Centron;	11 11150.		
chromanyl)	Choice-7;			
phenoxy) ethyl]-,	centchrom			
trans-	an;			
	Saheli			
2-Oxapregna-4,6-	osaterone	Teikoku	EP 193871	
diene-3,20-	acetate;	Hormone		
dione, 17-	Hipros;	ļ	}	
(acetyloxy)-6-	TZP-4238			
chloro-				
Pregn-4-ene-	progester	Columbi		
3,20-dione	one;	a		
	Crinone	Laborat		
		ories		
Sulfamide, N,N-	quinagol-	Novarti	EP 77754	
diethyl-N'-	ide; CV-	s		
(1,2,3,4,4a,5,10	205-502;			
,10a-octahydro-	Nor-			
6-hydroxy-1-	prolac;			
propylbenzo[g]qu	SDZ-205-			
inolin-3-yl)-,	502			
(3alpha, 4aalpha,				
10abeta) - (+/-) - L-Proline, 1-	ramara	Translant	TD 451701	
(N2-(N-(N-(N-(N-	ramore- lix; Hoe-	Hoechst	EP 451791	
1	i i	Marion		
(N-(N-(N-acetyl- 3-(2-	013; Hoe- 013C;	Roussel		
naphthalenyl)-D-	Hoe-2013			
alanyl)-4-chl				
oro-D-				
phenylalanyl)-D-				
tryptophyl)-L-				
seryl)-L-				
tyrosyl)-0-(6-				
deoxy-alpha-L-				
mannopyra				
nosyl)-D-seryl)-				
L-leucyl)-L-				
arginyl)-, 2-				
(aminocarbonyl)h				

G 3			TT 5	Т
Compound	Common	Company	Reference	Dosage
	Name/			
	Trade			
	Name			
ydrazide-				
	somatosta	Tulane		
	tin	Univers		
	analogues	ity		
Ethanamine, 2-	tamoxi-	Zeneca	US 4536516	
[4-(1,2-	fen;		}	
diphenyl-1-	Ceadan;			
butenyl)phenoxy]	ICI-			
-N,N-dimethyl-,	46474;	į		
(Z) -	Kessar;	İ		ļ
	Nolgen;			
	Nolvadex;			
	Tafoxen;			·
	Tamofen;			
	Tamoplex;	}		
	Tamoxas-			
	ta;	İ		
	Tamoxen;			
	Tomaxen			
	tamoxifen	Pharmos		<del></del>
	methiod-		İ	
	iđe			}
Ethanamine, 2-	tamoxifen	Douglas		
[4-(1,2-				
diphenyl-1-				
butenyl)phenoxy]				
-N,N-dimethyl-,				:
(z)-				
D-Alaninamide,	tevere-	Asta		
N-acetyl-3-(2-	lix;	Medica		
naphthalenyl)-D-	Antarelix			
alanyl-4-chloro-				
D-pheny lalanyl-				
3-(3-pyridinyl)-				
D-alanyl-L-				
seryl-L-tyrosyl-				
N6-				
(aminocarbonyl)-				
D-lysyl-L -				
leucyl-N6-(1-			[.	
methylethyl)-L-				
lysyl-L-prolyl-				
Ethanamine, 2-	toremif-	Orion	EP 95875	60mg po

Compound	Common Name/ Trade Name	Company	Reference	Dosage
[4-(4-chloro- 1,2-diphenyl-1- butenyl)phenoxy] -N,N-dimethyl-, (Z)-	ene; Estrimex; Fareston; FC-1157; FC-1157a; NK-622	Pharma		
Luteinizing hormone- releasing factor (pig), 6-D- tryptophan-	tripto- relin; ARVEKAP; AY-25650; BIM- 21003; BN-52104; Decap- eptyl; WY-42422	Debio- pharm	US 4010125	
L- Tryptophanamide, D-phenylalanyl- L-cysteinyl-L- tyrosyl-D- tryptophyl-L- lysyl- L-valyl- L-cysteinyl-, cyclic (2-7)- disulfide-	vapreot- ide; BMY- 41606; Octasta- tin; RC- 160	Debio- pharm	EP 203031	500microg sc tid
1H- Benzotriazole, 6-[(4- chlorophenyl)- 1H-1,2,4- triazol-1- ylmethyl]-1- methyl-	vorozole; R-76713; R-83842; Rivizor	Johnson & Johnson	EP 293978	2.5mg/day

A sixth family of antineoplastic agents which may be used in combination with the present invention consists of a miscellaneous family of antineoplastic agents including, but not limited to alpha-carotene, alpha-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile,

amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron,

- benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristo-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, calcium carbonate, Calcet, Calci-Chew, Calci-Mix, Roxane calcium carbonate tablets, caracemide, carmethizole hydrochloride,
- Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Cell Pathways CP-461, Yakult
- Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, DFMO, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75,
- Daiichi Seiyaku DN-9693, docetaxel, Encore
  Pharmaceuticals E7869, elliprabin, elliptinium acetate,
  Tsumura EPMTC, ergotamine, etoposide, etretinate,
  Eulexin®, Cell Pathways Exisulind® (sulindac sulphone or
  CP-246), fenretinide, Merck Research Labs Finasteride,
- 25 Florical, Fujisawa FR-57704, gallium nitrate, gemcitabine, genkwadaphnin, Gerimed, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187,
- 30 ilmofosine, irinotecan, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, ketoconazole, Otsuak K-

76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leucovorin, levamisole, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, Materna, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, megestrol, merbarone, merocyanine derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone, Monocal, mopidamol, motretinide, Zenyaku Kogyo MST-16, Mylanta, N-(retinoyl)amino acids, Nilandron; Nisshin Flour Milling N-021, N-acylated-dehydroalanines, nafazatrom, 10 Taisho NCU-190, Nephro-Calci tablets, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, octreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, paclitaxel, pancratistatin, pazelliptine, Warner-Lambert PD-111707, 15 Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, retinoids, Encore 20 Pharmaceuticals R-flurbiprofen, Sandostatin; Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, Scherring-Plough SC-57050, Scherring-Plough SC-57068, selenium(selenite and selenomethionine), SmithKline 25 SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, Sugen SU-101, Sugen SU-5416, Sugen SU-6668, 30 sulindac, sulindac sulfone; superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides, Yamanouchi YM-534, Zileuton, ursodeoxycholic acid, and Zanosar.

Preferred miscellaneous agents that may be used in the present invention include, but are not limited to, those identified in Table No. 11, below.

Table No. 11. Miscellaneous agents

Compound	Common	Company	Reference	Dosage
	Name/			
	Trade Name			
Flutamide; 2-	EULEXIN®	Schering		750 mg/d in
methyl- N-(4-		Corp		3 8-hr
nitro-3-				doses.
(trifluoro-				
methyl)phenyl)	,			
propanamide				
	Ketocon-		US 4144346	
	azole			
	leucovo-		US 4148999	
	rin			
	irinote-		US 4604463	
	can		·	
	levamis-	-	GB 11/20406	
	ole			
	megestrol		US 4696949	
	paclita-		US 5641803	
	xel			
Nilutamide	Nilandron	Hoechst		A total
5,5-dimethyl		Marion		daily dose
3-(4-nitro 3-		Roussel		of 300 mg
(trifluorometh				for 30 days
yl) phenyl)				followed
2,4-				thereafter
imidazolidined				by three

Compound	Common	Company	Reference	Dosage
	Name/			
	Trade Name	·		
ione				tablets (50 mg each) once a day for a total daily dosage of 150 mg.
	Vinorel-		EP 0010458	
	bine			
	vinblas-			
	tine			
	vincris- tine	i		
Octreotide acetate L- cysteinamide, D- phenylalanyl- L-cysteinyl-L- phenylalanyl- D-tryptophyl- L-lysyl-L- threonyl- NSAIDs-(2- hydroxy-1- (hydroxymethyl )propyl)-, cyclic- disulfide; (R- (R*,R*) acetate salt	Sandosta- tin	Sandoz Pharma- ceuticals		s.c. or i.v. administrat ion Acromegaly: 50 - 300 mcgm tid. Carcinoid tumors: 100 - 600 mcgm/d (mean = 300 mcgm/d) Vipomas: 200-300 mcgm in first two weeks of therapy
Streptozocin Streptozocin 2-deoxy-2- (((methylnitro samino)carbony 1)amino)- alpha(and beta)-D- glucopyranose)	Zanosar	Pharmacia & Upjohn		i.v. 1000 mg/M2 of body surface per week for two weeks.
	topotecan		US 5004758	
Selenium			EP 804927	

Compound	Common Name/ Trade Name	Company	Referenc	Dosage
L- selenomethioni ne	ACES®	J.R. Carlson Laborat- ories		·
calcium carbonate sulindac	Exisuland®		US 5858694	
sulfone ursodeoxycho lic acid			US 5843929	
	Cell Pathways CP-461			·

Some additional preferred antineoplastic agents include those described in the individual patents listed in Table No. 12 below, and are hereby individually incorporated by reference.

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Table No. 12. Antineoplastic agents

EP	0296749	EP 0882734	EP 00253738	GB 02/135425
WO	09/832762	EP 0236940	บร 5338732	US 4418068
US	4692434	US 5464826	US 5061793	EP 0702961
EP	0702961	EP 0702962	EP 0095875	EP 0010458
EP	0321122	US 5041424	JP 60019790	WO 09/512606
US	4,808614	US 4526988	CA 2128644	US 5455270
WO	99/25344	WO 96/27014	US 5695966	DE 19547958
WO	95/16693	WO 82/03395	ປຣ 5789000	US 5902610
EP	189990	US 4500711	FR 24/74032	US 5925699
WO	99/25344	US 4537883	US 4808614	US 5464826
US	5366734	US 4767628	US 4100274	US 4584305
US	4336381	JP 5050383	JP 5050384	JP 5064281
JP	51146482	JP 5384981	US 5472949	US 5455270
US	4140704	US 4537883	US 4814470	US 3590028

PCT/US99/30776

US	4564675	US 4526988	US 4100274	US 4604463
US	4144346	US 4749713	US 4148999	GB 11/20406
US	4696949	US 4310666	US 5641803	US 4418068
US	5,004758	EP 0095875	EP 0010458	US 4935437
US	4,278689	US 4820738	US 4413141	US 5843917
US	5,858694	US 4330559	US 5851537	US 4499072
US	5,217886	WO 98/25603	WO 98/14188	

Table No. 13 provides illustrative examples of median dosages for selected cancer agents that may be used in combination with an antiangiogenic agent. It

5 should be noted that specific dose regimen for the chemotherapeutic agents below depends upon dosing considerations based upon a variety of factors including the type of neoplasia; the stage of the neoplasm; the age, weight, sex, and medical condition of the patient;

10 the route of administration; the renal and hepatic function of the patient; and the particular combination employed.

Table No. 13. Median dosages for selected cancer 15 agents.

	NAME OF CHEMOTHERAPEUTIC	
	AGENT	MEDIAN DOSAGE
20	Asparaginase	10,000 units
	Bleomycin Sulfate	15 units
	Carboplatin	50-450 mg.
	Carmustine	100 mg.
	Cisplatin	10-50 mg.

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	Cladribine	10 mg.
	Cyclophosphamide	100 mg2 gm.
	(lyophilized)	
	Cyclophosphamide (non-	100 mg2 gm.
5	lyophilized)	
	Cytarabine (lyophilized	100 mg2 gm.
	powder)	
	Dacarbazine	100 mg200 mg.
	Dactinomycin	0.5 mg.
10	Daunorubicin	20 mg.
	Diethylstilbestrol	250 mg.
	Doxorubicin	10-150 mg.
	Etidronate	300 mg.
	Etoposide	100 mg.
15	Floxuridine	500 mg.
	Fludarabine Phosphate	50 mg.
	Fluorouracil	500 mg5 gm.
	Goserelin	3.6 mg.
	Granisetron Hydrochloride	1 mg.
20	Idarubicin	5-10  mg.
	Ifosfamide	1-3 gm.
	Leucovorin Calcium	50-350 mg.
	Leuprolide	3.75-7.5 rng.
	Mechlorethamine	10 mg.
25	Medroxyprogesterone	1 gm.
	Melphalan	50 gm.
	Methotrexate	20 mg1 gm.
	Mitomycin	5-40  mg.
	Mitoxantrone	20-30  mg.
30	Ondansetron Hydrochloride	40 mg.
	Paclitaxel	30 mg.

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	Pamidronate Disodium	30-90 mg.
	Pegaspargase	750 units
	Plicamycin	2,500 mcgm.
	Streptozocin	1 gm.
5	Thiotepa	15 mg.
	Teniposide	50 mg.
	Vinblastine	10 mg.
	Vincristine	1-5 mg.
	Aldesleukin	22 million units
10	Epoetin Alfa	2,000-10,000 units
	Filgrastim	300-480 mcgm.
	Immune Globulin	500 mg10 gm.
	Interferon Alpha-2a	3-36 million units
	Interferon Alpha-2b	3-50 million units
15	Levamisole	50 mg.
	Octreotide	1,000-5,000 mcgm.
	Sargramostim	250-500 mcgm.

The anastrozole used in the therapeutic

combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,935,437.

The capecitabine used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,472,949.

The carboplatin used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,455,270.

The Cisplatin used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,140,704.

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The cyclophosphamide used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,537,883.

The eflornithine (DFMO) used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,413,141.

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The docetaxel used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,814,470.

10 The doxorubicin used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 3,590,028.

The etoposide used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,564,675.

The fluorourical used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,336,381.

The gemcitabine used in the therapeutic

combinations of the present invention can be prepared in
the manner set forth in U.S. Patent No. 4,526,988.

The goserelin used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,100,274.

25 The irinotecan used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,604,463.

The ketoconazole used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,144,346.

The letrozole used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,749,713.

The leucovorin used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,148,999.

The levamisole used in the therapeutic combinations of the present invention can be prepared in the manner set forth in GB 11/20,406.

The megestrol used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,696,949.

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The mitoxantrone used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,310,666.

The paclitaxel used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,641,803.

The Retinoic acid used in the therapeutic

combinations of the present invention can be prepared in
the manner set forth in U.S. Patent No. 4,843,096.

The tamoxifen used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,418,068.

The topotecan used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,004,758.

The toremifene used in the therapeutic combinations of the present invention can be prepared in the manner set forth in EP 00/095,875.

The vinorelbine used in the therapeutic combinations of the present invention can be prepared in the manner set forth in EP 00/010,458.

The sulindac sulfone used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,858,694.

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The selenium (selenomethionine) used in the therapeutic combinations of the present invention can be prepared in the manner set forth in EP 08/04,927.

The ursodeoxycholic acid used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 97/34,608. Ursodeoxycholic acid can also be prepared according to the manner set forth in EP 05/99,282. Finally, ursodeoxycholic acid can be prepared according to the manner set forth in U.S. Patent No. 5,843,929.

anastrozole, calcium carbonate, capecitabine,
carboplatin, cisplatin, Cell Pathways CP-461,

cyclophosphamide, docetaxel, doxorubicin, etoposide,
Exisulind®, fluorouracil (5-FU), fluoxymestrine,
gemcitabine, goserelin, irinotecan, ketoconazole,
letrozol, leucovorin, levamisole, megestrol,
mitoxantrone, paclitaxel, raloxifene, retinoic acid,

tamoxifen, thiotepa, topotecan, toremifene, vinorelbine,
vinblastine, vincristine, selenium (selenomethionine),
ursodeoxycholic acid, sulindac sulfone and eflornithine
(DFMO).

The phrase "taxane" includes a family of diterpene
alkaloids all of which contain a particular eight (8)
member "taxane" ring structure. Taxanes such as

paclitaxel prevent the normal post division breakdown of microtubules which form to pull and separate the newly duplicated chromosome pairs to opposite poles of the cell prior to cell division. In cancer cells which are 5 rapidly dividing, taxane therapy causes the microtubules to accumulate which ultimately prevents further division of the cancer cell. Taxane therapy also affects other cell processes dependant on microtubules such as cell motility, cell shape and intracellular transport. The major adverse side-effects associated with taxane 10 therapy can be classified into cardiac effects, neurotoxicity, haematological toxicity, and hypersensitivity reactions. (See Exp. Opin. Thera. Patents (1998) 8(5), hereby incorporated by reference). 15 Specific adverse side-effects include neutropenia, alopecia, bradycardia, cardiac conduction defects, acute hypersensitivity reactions, neuropathy, mucositis, dermatitis, extravascular fluid accumulation,

alopecia, bradycardia, cardiac conduction defects, acute hypersensitivity reactions, neuropathy, mucositis, dermatitis, extravascular fluid accumulation, arthralgias, and myalgias. Various treatment regimens have been developed in an effort to minimize the side effects of taxane therapy, but adverse side-effects remain the limiting factor in taxane therapy.

It has been recently discovered in vitro that COX-2 expression is elevated in cells treated with taxanes.

25 Elevated levels of COX-2 expression are associated with inflammation and generation of other COX-2 derived prostaglandin side effects. Consequently, when taxane therapy is provided to a patient, the administration of a COX-2 inhibitor is contemplated to reduce the inflammatory and other COX-2 derived prostaglandin side effects associated with taxane therapy.

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Taxane derivatives have been found to be useful in treating refractory ovarian carcinoma, urothelial cancer, breast carcinoma, melanoma, non-small-cell lung carcinoma, gastric, and colon carcinomas, squamous carcinoma of the head and neck, lymphoblastic, myeloblastic leukemia, and carcinoma of the esophagus.

mg/m<sup>2</sup> dose over a 6 to 24 hour infusion. For renal cell carcinoma, squamous carcinoma of head and neck,

10 carcinoma of esophagus, small and non-small cell lung cancer, and breast cancer, paclitaxel is typically administered as a 250 mg/m<sup>2</sup> 24 hour infusion every 3 weeks. For refractory ovarian cancer paclitaxel is typically dose escalated starting at 110 mg/m<sup>2</sup>.

Docetaxel is typically administered in a 60 - 100 mg/M² i.v. over 1 hour, every three weeks. It should be noted, however, that specific dose regimen depends upon dosing considerations based upon a variety of factors including the type of neoplasia; the stage of the neoplasm; the age, weight, sex, and medical condition of the patient; the route of administration; the renal and hepatic function of the patient; and the particular agents and combination employed.

In one embodiment, paclitaxel is used in the

25 present invention in combination with a cyclooxygenase-2
inhibitor and a MMP inhibitor and with cisplatin,
cyclophosphamide, or doxorubicin for the treatment of
breast cancer. In another embodiment paciltaxel is used
in combination with a cyclooxygenase-2 inhibitor and a

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MMP inhibitor, cisplatin or carboplatin, and ifosfamide for the treatment of ovarian cancer.

In another embodiment docetaxal is used in the present invention in combination with a cyclooxygenase-2 inhibitor and a MMP inhibitor and in combination with cisplatin, cyclophosphamide, or doxorubicin for the treatment of ovary and breast cancer and for patients with locally advanced or metastatic breast cancer who have progressed during anthracycline based therapy.

The following references listed in Table No. 14 below, hereby individually incorporated by reference herein, describe various taxanes and taxane derivatives suitable for use in the present invention, and processes for their manufacture.

15 Table No. 14. Taxanes and taxane derivatives

EP 694539	EP 683232	EP 639577	EP 627418
EP 604910	EP 797988	EP 727492	EP 767786
EP 767376	US 5886026	US 5880131	US 5879929
US 5871979	US 5869680	US 5871979	US 5854278
US 5840930	US 5840748	US 5827831	US 5824701
US 5821363	US 5821263	US 5811292	US 5808113
US 5808102	US 5807888	US 5780653	US 5773461
US 5770745	US 5767282	US 5763628	US 5760252
US 5760251	US 5756776	บร 5750737	US 5744592
US 5739362	US 5728850	US 5728725	US 5723634
US 5721268	US 5717115	US 5716981	US 5714513
US 5710287	US 5705508	US 5703247	US 5703117
US 5700669	US 5693666	บร 5688977	US 5684175
US 5683715	บร 5679807	US 5677462	US 5675025
US 5670673	US 5654448	US 5654447	US 5646176
US 5637732	US 5637484	US 5635531	US 5631278

US 5616739 US 5614645 US 5614549 US 5608102 US 5599820 US 5594157 US 5587489 US 5580899 US 5574156 US 5567614 US 5565478 US 5560872 US 5556878 US 5547981 US 5539103 US 5532363 US 5530020 US 5508447 US 5489601 US 5484809 US 5475011 US 5473055 US 5470866 US 5466834 US 5449790 US 5442065 US 5440056 US 5430160 US 5412116 US 5412092 US 5411984 US 5407816 US 5407674 US 5405972 US 5399726 US 5395850 US 5384399 US 5380916 US 5380751 US 5367086 US 5356928 US 5356927 US 5352806 US 5350866 US 5344775 US 5338872 US 5336785 US 5319112 US 5296506 US 5294737 US 5294637 US 5284865 US 5284864 US 5283253 US 5279949 US 5274137 US 5274124 US 5272171 US 5254703 US 5254580 US 5250683 US 5243045 US 5229526 US 5227400 US 5015744 WO 98/38862 WO 95/24402 WO 93/2117 EP 681574 EP 681575 EP 568203 EP 642503 EP 667772 EP 668762 EP 679082 EP 681573 EP 688212 EP 690712 EP 690853 EP 710223 EP 534708 EP 534709 EP 605638 EP 428376				
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US 5556878 US 5547981 US 5539103 US 5532363 US 5530020 US 5508447 US 5489601 US 5484809 US 5475011 US 5473055 US 5470866 US 5466834 US 5449790 US 5442065 US 5440056 US 5430160 US 5412116 US 5412092 US 5411984 US 5407816 US 5407674 US 5405972 US 5399726 US 5395850 US 5384399 US 5380916 US 5380751 US 5367086 US 5356928 US 5356927 US 5352806 US 5350866 US 5344775 US 5338872 US 5336785 US 5319112 US 5296506 US 5294737 US 5294637 US 5284865 US 5284864 US 5283253 US 5279949 US 5274137 US 5274124 US 5272171 US 5254703 US 5254580 US 5250683 US 5243045 US 5229526 US 5227400 US 5015744 WO 98/38862 WO 95/24402 WO 93/2117 EP 681574 EP 681575 EP 568203 EP 642503 EP 667772 EP 668762 EP 679082 EP 681573 EP 688212 EP 690712 EP 690853 EP 710223 EP 534708 EP 534709 EP 605638 EP 669918	US 5599820	US 5594157	US 5587489	US 5580899
US 5530020 US 5508447 US 5489601 US 5484809 US 5475011 US 5473055 US 5470866 US 5466834 US 5449790 US 5442065 US 5440056 US 5430160 US 5412116 US 5412092 US 5411984 US 5407816 US 5407674 US 5405972 US 5399726 US 5395850 US 5384399 US 5380916 US 5380751 US 5367086 US 5356928 US 5356927 US 5352806 US 5350866 US 5344775 US 5338872 US 5336785 US 5319112 US 5296506 US 5294737 US 5294637 US 5284865 US 5274124 US 5272171 US 5254703 US 5274137 US 5274124 US 5272171 US 5254703 US 5254580 US 5200534 US 5194635 US 5175,315 US 5136060 US 5015744 WO 98/38862 WO 95/24402 WO 93/2117 EP 681574 EP 681575 EP 568203 EP 642503 EP 667772 EP 668762 EP 679082 EP 681573 EP 688212 EP 690712 EP 690853 EP 710223 EP 534708 EP 534709 EP 605638 EP 669918 EP 855909 EP 605638 EP 428376 EP 428376	US 5574156	US 5567614	US 5565478	US 5560872
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US 5449790 US 5442065 US 5440056 US 5430160 US 5412116 US 5412092 US 5411984 US 5407816 US 5407674 US 5405972 US 5399726 US 5395850 US 5384399 US 5380916 US 5380751 US 5367086 US 5356928 US 5356927 US 5352806 US 5350866 US 5344775 US 5338872 US 5336785 US 5319112 US 5296506 US 5294737 US 5294637 US 5284865 US 5284864 US 5283253 US 5279949 US 5274137 US 5274124 US 5272171 US 5254703 US 5254580 US 5250683 US 5243045 US 5229526 US 5227400 US 5015744 WO 98/38862 WO 95/24402 WO 93/2117 EP 681574 EP 681575 EP 568203 EP 642503 EP 667772 EP 668762 EP 679082 EP 681573 EP 688212 EP 690712 EP 690853 EP 710223 EP 534708 EP 534709 EP 605638 EP 669918 EP 855909 EP 605638 EP 428376 EP 428376	บร 5530020	US 5508447	US 5489601	US 5484809
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US 5284864 US 5283253 US 5279949 US 5274137 US 5274124 US 5272171 US 5254703 US 5254580 US 5250683 US 5243045 US 5229526 US 5227400 US 5200534 US 5194635 US 5175,315 US 5136060 US 5015744 WO 98/38862 WO 95/24402 WO 93/2117 EP 681574 EP 681575 EP 568203 EP 642503 EP 667772 EP 668762 EP 679082 EP 681573 EP 688212 EP 690712 EP 690853 EP 710223 EP 534708 EP 534709 EP 605638 EP 669918 EP 855909 EP 605638 EP 428376 EP 428376	US 5344775	US 5338872	US 5336785	บร 5319112
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US 5250683 US 5243045 US 5229526 US 5227400 US 5200534 US 5194635 US 5175,315 US 5136060 US 5015744 WO 98/38862 WO 95/24402 WO 93/2117 EP 681574 EP 681575 EP 568203 EP 642503 EP 667772 EP 668762 EP 679082 EP 681573 EP 688212 EP 690712 EP 690853 EP 710223 EP 534708 EP 534709 EP 605638 EP 669918 EP 855909 EP 605638 EP 428376 EP 428376	US 5284864	US 5283253	US 5279949	US 5274137
US 5200534 US 5194635 US 5175,315 US 5136060 US 5015744 WO 98/38862 WO 95/24402 WO 93/2117 EP 681574 EP 681575 EP 568203 EP 642503 EP 667772 EP 668762 EP 679082 EP 681573 EP 688212 EP 690712 EP 690853 EP 710223 EP 534708 EP 534709 EP 605638 EP 669918 EP 855909 EP 605638 EP 428376 EP 428376	US 5274124	US 5272171	US 5254703	US 5254580
US 5015744 WO 98/38862 WO 95/24402 WO 93/2117 EP 681574 EP 681575 EP 568203 EP 642503 EP 667772 EP 668762 EP 679082 EP 681573 EP 688212 EP 690712 EP 690853 EP 710223 EP 534708 EP 534709 EP 605638 EP 669918 EP 855909 EP 605638 EP 428376 EP 428376	US 5250683	US 52430 <b>4</b> 5	บร 5229526	US 5227400
EP 681574       EP 681575       EP 568203       EP 642503         EP 667772       EP 668762       EP 679082       EP 681573         EP 688212       EP 690712       EP 690853       EP 710223         EP 534708       EP 534709       EP 605638       EP 669918         EP 855909       EP 605638       EP 428376       EP 428376	US 5200534	US 5194635	US 5175,315	US 5136060
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EP 688212       EP 690712       EP 690853       EP 710223         EP 534708       EP 534709       EP 605638       EP 669918         EP 855909       EP 605638       EP 428376       EP 428376	EP 681574	EP 681575	EP 568203	EP 642503
EP 534708 EP 534709 EP 605638 EP 669918 EP 855909 EP 605638 EP 428376 EP 428376	EP 667772	EP 668762	EP 679082	EP 681573
EP 855909 EP 605638 EP 428376 EP 428376	EP 688212	EP 690712	EP 690853	EP 710223
	EP 534708	EP 534709	EP 605638	EP 669918
ED 534707   ED 605637   ED 679156   ED 689436	EP 855909	EP 605638	EP 428376	EP 428376
EF 554707 EF 605057 EF 675150 22 605150	EP 534707	EP 605637	EP 679156	EP 689436
EP 690867 EP 605637 EP 690867 EP 687260	EP 690867	EP 605637	EP 690867	EP 687260
EP 690711 EP 400971 EP 690711 EP 400971	EP 690711	EP 400971	EP 690711	EP 400971
EP 690711 EP 884314 EP 568203 EP 534706	EP 690711	EP 884314	EP 568203	EP 534706
EP 428376 EP 534707 EP 400971 EP 669918	EP 428376	EP 534707	EP 400971	EP 669918
EP 605637 US 5015744 US 5175315 US 5243045	EP 605637	US 5015744	US 5175315	US 5243045

US 5283253	US 5250683	US 5254703	US 5274124
US 5284864	US 5284865	US 5350866	US 5227400
US 5229526	US 4876399	US 5136060	US 5336785
US 5710287	US 5714513	US 5717115	US 5721268
US 5723634	US 5728725	US 5728850	US 5739362
US 5760219	US 5760252	US 5384399	บร 5399726
US 5405972	US 5430160	US 5466834	US 5489601
US 5532363	US 5539103	US 5574156	US 5587489
US 5618952	US 5637732	US 5654447	US 4942184
US 5059699	US 5157149	US 5202488	បន 5750736
US 5202488	US 5549830	US 5281727	US 5019504
US 4857653	US 4924011	US 5733388	US 5696153
WO 93/06093	WO 93/06094	WO 94/10996	WO 9/10997
WO 94/11362	WO 94/15599	WO 94/15929	WO 94/17050
WO 94/17051	WO 94/17052	WO 94/20088	WO 94/20485
WO 94/21250	WO 94/21251	WO 94/21252	WO 94/21623
WO 94/21651	WO 95/03265	WO 97/09979	WO 97/42181
WO 99/08986	WO 99/09021	WO 93/06079	US 5202448
US 5019504	US 4857653	US 4924011	WO 97/15571
WO 96/38138	US 5489589	EP 781778	WO 96/11683
EP 639577	EP 747385	US 5422364	WO 95/11020
EP 747372	WO 96/36622	US 5599820	WO 97/10234
WO 96/21658	WO 97/23472	US 5550261	WO 95/20582
WO 97/28156	WO 96/14309	WO 97/32587	WO 96/28435
WO 96/03394	WO 95/25728	WO 94/29288	WO 96/00724
WO 95/02400	EP 694539	WO 95/24402	WO 93/10121
WO 97/19086	WO 97/20835	WO 96/14745	WO 96/36335
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U.S. Patent No. 5,019,504 describes the isolation of paclitaxel and related alkaloids from culture grown Taxus brevifolia cells.

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- U.S. Patent No. 5,675,025 describes methods for synthesis of Taxol®, Taxol® analogues and intermediates from baccatin III.
- U.S. Patent No. 5,688,977 describes the synthesis

  of Docetaxel from 10-deacetyl baccatin III.
  - U.S. Patent No. 5,202,488 describes the conversion of partially purified taxane mixture to baccatin III.
  - U.S. Patent No. 5,869,680 describes the process of preparing taxane derivatives.
- 10 U.S. Patent No. 5,856,532 describes the process of the production of Taxol®.
  - U.S. Patent No. 5,750,737 describes the method for paclitaxel synthesis.
- U.S. Patent No. 6,688,977 describes methods for docetaxel synthesis.
  - U.S. Patent No. 5,677,462 describes the process of preparing taxane derivatives.
  - U.S. Patent No. 5,594,157 describes the process of making Taxol® derivatives.
- Some preferred taxanes and taxane derivatives are described in the patents listed in Table No. 15 below, and are hereby individually incorporated by reference herein.
- Table No. 15. Some preferred taxanes and taxane

  derivatives

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US 5015744	US 5136060	US 5175315	US 5200534
US 5194635	US 5227400	US 4924012	US 5641803
US 5059699	US 5157049	US 4942184	US 4960790
US 5202488	US 5675025	US 5688977	US 5750736
US 5684175	US 5019504	US 4814470	WO 95/01969

The phrase "retinoid" includes compounds which are

natural and synthetic analogues of retinol (Vitamin A). The retinoids bind to one or more retinoic acid receptors to initiate diverse processes such as reproduction, development, bone formation, cellular proliferation and differentiation, apoptosis, hematopoiesis, immune function and vision. Retinoids are required to maintain normal differentiation and 10 proliferation of almost all cells and have been shown to reverse/suppress carcinogenesis in a variety of in vitro and in vivo experimental models of cancer, see (Moon et al., Ch. 14 Retinoids and cancer. In The Retinoids, Vol. 2. Academic Press, Inc. 1984). Also see Roberts et al. 15 Cellular biology and biochemistry of the retinoids. In The Retinoids, Vol. 2. Academic Press, Inc. 1984, hereby incorporated by reference), which also shows that vesanoid (tretinoid trans retinoic acid) is indicated for induction of remission in patients with acute 20 promyelocytic leukemia (APL).

A synthetic description of retinoid compounds, hereby incorporated by reference, is described in: Dawson MI and Hobbs PD. The synthetic chemistry of

retinoids: in The retinoids, 2<sup>nd</sup> edition. MB Sporn, AB Roberts, and DS Goodman(eds). New York: Raven Press, 1994, pp 5-178.

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Lingen et al. describe the use of retinoic acid and interferon alpha against head and neck squamous cell carcinoma (Lingen, MW et al., Retinoic acid and interferon alpha act synergistically as antiangiogenic and antitumor agents against human head and neck squamous cell carcinoma. Cancer Research 58 (23) 5551-5558 (1998), hereby incorporated by reference).

Iurlaro et al. describe the use of beta interferon and 13-cis retinoic acid to inhibit angiogenesis.

(Iurlaro, M et al., Beta interferon inhibits HIV-1 Tatinduced angiogenesis: synergism with 13-cis retinoic acid. European Journal of Cancer 34 (4) 570-576 (1998), hereby incorporated by reference).

Majewski et al. describe Vitamin D3 and retinoids in the inhibition of tumor cell-induced angiogenesis. (Majewski, S et al., Vitamin D3 is a potent inhibitor of tumor cell-induced angiogenesis. J. Invest. Dermatology. Symposium Proceedings, 1 (1), 97-101 (1996), hereby incorporated by reference.

Majewski et al. describe the role of retinoids and other factors in tumor angiogenesis. Majewski, S et al., Role of cytokines, retinoids and other factors in tumor angiogenesis. Central-European journal of Immunology 21 (4) 281-289 (1996), hereby incorporated by reference).

Bollag describes retinoids and alpha-interferon in the prevention and treatment of neoplastic disease.

30 (Bollag W. Retinoids and alpha-interferon in the prevention and treatment of preneoplastic and neoplastic

diseases. Chemotherapie Journal, (Suppl) 5 (10) 55-64 (1996), hereby incorporated by reference.

Bigg, HF et al. describe all-trans retinoic acid with basic fibroblast growth factor and epidermal growth factor to stimulate tissue inhibitor of metalloproteinases from fibroblasts. (Bigg, HF et al., All-trans-retoic acid interacts synergystically with basic fibroblast growth factor and epidermal growth factor to stimulate the production of tissue inhibitor of metalloproteinases from fibroblasts. Arch. Biochem. Biophys. 319 (1) 74-83 (1995), hereby incorporated by reference).

Nonlimiting examples of retinoids that may be used in the present invention are identified in Table No. 16 below.

Table No. 16. Retinoids

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Compound	Common Name/Trade Name	Company	Reference	Dosage
CD-271	Adapaline		EP 199636	
Tretinoin	Vesanoid	Roche		45
trans		Holdings		mg/M²/day
retinoic				as two
acid				evenly
				divided
				doses
				until
			•	complete
				remission
2,4,6,8-	etretinate	Roche	US	.25 - 1.5
Nonatetraen	isoetret-	Holdings	4215215	mg/kg/day
oic acid,	in; Ro-10-			

		<del></del>	T	T
9-(4-	9359; Ro-			
methoxy-	13-7652;			
2,3,6-	Tegison;			
trimethylph	Tigason			
enyl)-3,7-				
dimethyl- ,				
ethyl				
ester,				
(all-E)-				
Retinoic	isotret-	Roche	US 4843096	.5 to 2
acid, 13-	inoin	Holdings		mg/kg/day
cis-	Accutane;			
	Isotrex;			
	Ro-4-3780;			
	Roaccutan;			
	Roaccutane			
	Roche Ro-	Roche		
	40-0655	Holdings		
	Roche Ro-	Roche		
	25-6760	Holdings		
	Roche Ro-	Roche		
	25-9022	Holdings		
	Roche Ro-	Roche		
	25-9716	Holdings		
Benzoic	TAC-101	Taiho		
acid, 4-		Pharmace		
[[3,5-		utical		
bis(trimeth				
ylsilyl)ben				
zoyl]amino]				

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Retinamide,	fenretinid			50 - 400
N-(4-	e 4-HPR;			mg/kg/day
hydroxyphen	·			g, 1.g, uu
yl)-	R-1967			
(2E,4E,6E)-		Ligand		20
7-(3,5-Di-	ALRT-1550;	Pharma-		microg/m2
tert-	ALRT-550;	ceuticas		
butylphenyl				/day to
)-3-	LG-1550	,		
		Allergan		microg/m2
methylocta-		USA		/day
2,4,6-				administe
trienoic				red as a
acid	i			single
				daily
				oral dose
	Molecular		US	
	Design		4885311	
	MDI-101			
	Molecular		US	
	Design		4677120	
	MDI-403			
Benzoic	bexarotene		WO	
acid, 4-(1-	LG-1064;		94/15901	
(5,6,7,8-	LG-1069;			
tetrahydro-	LGD-1069;			
3,5,5,8,8-	Targretin;			
pentamethyl	Targretin			
-2-	Oral;			
naphthaleny	Targretin			
1)eth	Topical			

enyl)-	Gel			
Benzoic	bexarotene	R P		
acid, 4-(1-	, soft gel	Scherer		
(5,6,7,8-	bexarotene			
tetrahydro-	, Ligand;			
3,5,8,8-	bexaroten			
pentamethyl				
-2-			:	
naphthaleny				
1)ethen				
yl)-				
(2E,4E)-3-			WO	
methyl-5-			96/05165	
[3-				
(5,5,8,8-				
tetramethyl				
-5,6,7,8-				
tetrahydro-				
naphthalen-				
2-y1)-				
thiopen-2-				
yl]-penta-				
2,4-dienoic				
acid				
	SR-11262	Hoffmann		
	F	-La		
		Roche		
		Ltd		
	BMS-181162	Bristol	EP 476682	
		Myers		
		Squibb		

N- (4-	IIT		Cancer	
hydroxyphen	Research		Research	
yl)retinami	Institute		39, 1339-	
de			1346	
			(1979)	
	7 ON 102174			
·	AGN-193174	Allergan	WO	
		USA	96/33716	

The following individual patent references listed in Table No. 17 below, hereby individually incorporated by reference, describe various retinoid and retinoid derivatives suitable for use in the present invention described herein, and processes for their manufacture.

Table No. 17. Retinoids

WO 00/37107

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US 4215215	US 4885311	US 4677120	US 4105681
US 5260059	US 4503035	US 5827836	US 3878202
US 4843096	WO 96/05165	WO 97/34869	WO 97/49704
EP 19/9636	WO 96/33716	WO 97/24116	WO 97/09297
WO 98/36742	WO 97/25969	WO 96/11686	WO 94/15901
WO 97/24116	CH 61/6134	DE 2854354	EP 579915
US 5547947	EP 552624	EP 728742	EP 331983
EP 476682			

Some preferred retinoids include Accutane;

10 Adapalene; Allergan AGN-193174; Allergan AGN-193676;

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Allergan AGN-193836; Allergan AGN-193109; Aronex AR-623; BMS-181162; Galderma CD-437; Eisai ER-34617; Etrinate; Fenretinide; Ligand LGD-1550; lexacalcitol; Maxia Pharmaceuticals MX-781; mofarotene; Molecular Design MDI-101; Molecular Design MDI-301; Molecular Design MDI-403; Motretinide; Eisai 4-(2-[5-(4-methyl-7-ethylbenzofuran-2-yl)pyrrolyl]) benzoic acid; Johnson & Johnson N-[4-[2-thyl-1-(1H-imidazol-1-yl)butyl]phenyl]-2-benzothiazolamine; Soriatane; Roche SR-11262; Tocoretinate; Advanced Polymer Systems trans-retinoic acid; UAB Research Foundation UAB-8; Tazorac; TopiCare; Taiho TAC-101; and Vesanoid.

cGMP phosphodiesterase inhibitors, including Sulindac sulfone (Exisuland®) and CP-461 for example, are apoptosis inducers and do not inhibit the cyclooxygenase pathways. cGMP phosphodiesterase inhibitors increase apoptosis in tumor cells without arresting the normal cycle of cell division or altering the cell's expression of the p53 gene.

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Ornithine decarboxylase is a key enzyme in the polyamine synthesis pathway that is elevated in most tumors and premalignant lesions. Induction of cell growth and proliferation is associated with dramatic increases in ornithine decarboxylase activity and subsequent polyamine synthesis. Further, blocking the formation of polyamines slows or arrests growth in transformed cells. Consequently, polyamines are thought to play a role in tumor growth. Difluoromethylornithine (DFMO) is a potent inhibitor of ornithine decarboxylase that has been shown to inhibit carcinogen-induced cancer development in a variety of rodent models (Meyskens et

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al. Development of Difluoromethylornithine (DFMO) as a chemoprevention agent. Clin. Cancer Res. 1999 May, 5(%):945-951, hereby incorporated by reference, herein). DFMO is also known as 2-difluoromethyl-2,5-diaminopentanoic acid, or 2-difluoromethyl-2,5-diaminovaleric acid, or a-(difluoromethyl) ornithine; DFMO is marketed under the tradename Elfornithine®.

inhibitors is contemplated to treat or prevent cancer,
including but not limited to colon cancer or colonic
polyps.

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Therefore, the use of DFMO in combination with COX-2

Populations with high levels of dietary calcium have been reported to be protected from colon cancer. In vivo, calcium carbonate has been shown to inhibit colon cancer via a mechanism of action independent from COX-2 inhibition. Further, calcium carbonate is well tolerated. A combination therapy consisting of calcium carbonate and a selective COX-2 inhibitor is contemplated to treat or prevent cancer, including but not limited to colon cancer or colonic polyps.

Several studies have focused attention on bile acids as a potential mediator of the dietary influence on colorectal cancer risk. Bile acids are important detergents for fat solubilization and digestion in the proximal intestine. Specific transprot processes in the apical domain of the terminal ileal enterocyte and basolateral domain of the hepatocyte account for the efficient conservation in the enterohepatic circulation. Only a small fraction of bile acids enter the colon; however, perturbations of the cycling rate of bile acids by diet (e.g. fat) or surgery may increase the fecal

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bile load and perhaps account for the associated increased risk of colon cancer. (Hill MJ, Bile flow and colon cancer. 238 Mutation Review, 313 (1990). Ursodeoxycholate (URSO), the hydrophilic 7-beta epimer of chenodeoxycholate, is non cytotoxic in a variety of 5 cell model systems including colonic epithelia. URSO is also virtually free of side effects. URSO, at doses of 15mg/kg/day used primarily in biliary cirrhosis trials were extremely well tolerated and without toxicity. (Pourpon et al., A multicenter, controlled trial of 10 ursodiol for the treatment of primary biliary cirrhosis. 324 New Engl. J. Med. 1548 (1991)). While the precise mechanism of URSO action is unknown, beneficial effects of URSO therapy are related to the enrichment of the hepatic bile acid pool with this hydrophilic bile acid. 15 It has thus been hypothesized that bile acids more hydrophilic than URSO will have even greater beneficial effects than URSO. For example, tauroursodeoxycholate (TURSO) the taurine conjugate of URSO. Non-steroidal anti-inflammatory drugs (NSAIDs) can inhibit the 20 neoplastic transformation of colorectal epithelium. The likely mechanism to explain this chemopreventive effect is inhibition of prostaglandin synthesis. NSAIDs inhibit cyclooxygenase, the enzyme that converts arachidonic acid to prostaglandins and thromboxanes. However, the 25 potential chemopreventive benefits of NSAIDs such as sulindac or mesalamine are tempered by their well known toxicities and moderately high risk of intolerance. Abdominal pain, dispepsia, nausea, diarrhea, constipation, rash, dizziness, or headaches have been 30 reported in up to 9% of patients. The elderly appear to

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be particularly vulnerable as the incidence of NSAID-induced gastroduodenal ulcer disease, including gastrointestinal bleeding, is higher in those over the age of 60; this is also the age group most likely to develop colon cancer, and therefore most likely to benefit from chemoprevention. The gastrointestinal side effects associated with NSAID use result from the inhibition of cyclooxygenase-1, an enzyme responsible for maintenance of the gastric mucosa. Therefore, the use of COX-2 inhibitors in combination with URSO is contemplated to treat or prevent cancer, including but not limited to colon cancer or colonic polyps; it is contemplated that this treatment will result in lower gastrointestinal side effects than the combination of standard NSAIDs and URSO.

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An additional class of antineoplastic agents that may be used in the present invention include nonsteroidal antiinflammatory drugs (NSAIDs). NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human 20 arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). However, for the purposes of the present invention the definition of an NSAID does not include the "cyclooxygenase-2 inhibitors" described herein. Thus the phrase "nonsteroidal antiinflammatory 25 drug" or "NSAID" includes agents that specifically inhibit cyclooxygenase-1, without significant inhibition of cyclooxygenase-2; or inhibit cyclooxygenase-1 and cyclooxygenase-2 at substantially the same potency; or inhibit neither cyclooxygenase-1 or cyclooxygenase-2. 30 The potency and selectivity for the enzyme

cyclooxygenase-1 and cyclooxygenase-2 can be determined by assays well known in the art, see for example, Cromlish and Kennedy, Biochemical Pharmacology, Vol. 52, pp 1777-1785, 1996.

Examples of NSAIDs that can be used in the combinations of the present invention include sulindac, indomethacin, naproxen, diclofenac, tolectin, fenoprofen, phenylbutazone, piroxicam, ibuprofen, ketophen, mefenamic acid, tolmetin, flufenamic acid, nimesulide, niflumic acid, piroxicam, tenoxicam, phenylbutazone, fenclofenac, flurbiprofen, ketoprofen, fenoprofen, acetaminophen, salicylate and aspirin.

The term "clinical tumor" includes neoplasms that are identifiable through clinical screening or diagnostic procedures including, but not limited to, palpation, biopsy, cell proliferation index, endoscopy, mammagraphy, digital mammography, ultrasonography, computed tomagraphy (CT), magnetic resonance imaging (MRI), positron emmission tomaagraphy (PET),

- radiography, radionuclide evaluation, CT- or MRI-guided aspiration cytology, and imaging-guided needle biopsy, among others. Such diagnostic techniques are well known to those skilled in the art and are described in Cancer Medicine 4<sup>th</sup> Edition, Volume One. J.F. Holland, R.C.
- 25 Bast, D.L. Morton, E. Frei III, D.W. Kufe, and R.R. Weichselbaum (Editors). Williams & Wilkins, Baltimore (1997).

The term "tumor marker" or "tumor biomarker" encompasses a wide variety of molecules with divergent characteristics that appear in body fluids or tissue in association with a clinical tumor and also includes

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tumor-associated chromosomal changes. Tumor markers fall primarily into three categories: molecular or cellular markers, chromosomal markers, and serological or serum markers. Molecular and chromosomal markers complement standard parameters used to describe a tumor (i.e. histopathology, grade, tumor size) and are used primarily in refining disease diagnosis and prognosis after clinical manifestation. Serum markers can often be measured many months before clinical tumor detection and are thus useful as an early diagnostic test, in patient monitoring, and in therapy evaluation.

# Molecular Tumor Markers

Molecular markers of cancer are products of cancer cells or molecular changes that take place in cells because of activation of cell division or inhibition of apoptosis. Expression of these markers can predict a cell's malignant potential. Because cellular markers are not secreted, tumor tissue samples are generally required for their detection. Non-limiting examples of molecular tumor markers that can be used in the present invention are listed in Table No. 1, below.

Table No. 1. Non-limiting Examples of Molecular Tumor
Markers

Tumor	Marker	-
Breast	p53	
Breast, Ovarian	ErbB-2/Her-2	
Breast	S phase and ploidy	
Breast	pS2	
Breast	MDR2	,
Breast	urokinase plasminogen activator	

Breast,	myc family
Colon, Lung	

# Chromosomal Tumor Markers

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Somatic mutations and chromosomal aberrations have been associated with a variety of tumors. Since the identification of the Philadelphia Chromosome by Nowel and Hungerford, a wide effort to identify tumor-specific chromosomal alterations has ensued. Chromosomal cancer markers, like cellular markers, are can be used in the diagnosis and prognosis of cancer. In addition to the diagnostic and prognostic implications of chromosomal alterations, it is hypothesized that germ-line mutations 10 can be used to predict the likelihood that a particular person will develop a given type of tumor. Non-limiting examples of chromosomal tumor markers that can be used in the present invention are listed in Table No. 2, below.

Table No. 2. Non-limiting Examples of Chromosomal Tumor Markers

Tumor	Marker
Breast	1p36 loss
Breast	6q24-27 loss
Breast	11q22-23 loss
Breast	11q13 amplification
Breast	TP53 mutation
Colon	Gain of chromosome 13
Colon	Deletion of short arm of chromosome 1
Lung	Loss of 3p
Lung	Loss of 13q
Lung	Loss of 17p

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Lung Loss of 9p

# Serological Tumor Markers

Serum markers including soluble antigens, enzymes and hormones comprise a third category of tumor markers. Monitoring serum tumor marker concentrations during therapy provides an early indication of tumor recurrence and of therapy efficacy. Serum markers are advantageous for patient surveillance compared to chromosomal and cellular markers because serum samples are more easily obtainable than tissue samples, and because serum assays can be performed serially and more rapidly. Serum tumor markers can be used to determine appropriate therapeutic doses within individual patients. For example, the efficacy of a combination regimen consisting of chemotherapeutic and antiangiogenic agents can be measured by monitoring the relevant serum cancer marker levels. Moreover, an efficacious therapy dose can be achieved by modulating the therapeutic dose so as to keep the particular serum tumor marker concentration stable or within the reference range, which may vary depending upon the indication. The amount of therapy can then be modulated specifically for each patient so as to minimize side effects while still maintaining stable, reference range tumor marker levels. Table No. 3 provides non-limiting examples of serological tumor markers that can be used in the present invention.

Table No. 3. Non-limiting Examples of Serum Tumor
Markers

Cancer Type	Mark r

Germ Cell Tumors	a-fetoprotein (AFP)
Germ Cell Tumors	human chorionic gonadotrophin
	(hCG)
Germ Cell Tumors	placental alkaline
	phosphatase (PLAP)
Germ Cell Tumors	lactate dehydrogenase (LDH)
Prostate	prostate specific antigen
	(PSA)
Breast	carcinoembryonic antigen
	(CEA)
Breast	MUC-1 antigen (CA15-3)
Breast	tissue polypeptide antigen
	(TPA)
Breast	tissue polypeptide specific
	antigen (TPS)
Breast	CYFRA 21.1
Breast	soluble <i>erb</i> -B-2
Ovarian	CA125
Ovarian	OVX1
Ovarian	cancer antigen CA72-4
Ovarian	TPA
Ovarian	TPS
Gastrointestinal	CD44v6
Gastrointestinal	CEA
Gastrointestinal	cancer antigen CA19-9
Gastrointestinal	NCC-ST-439 antigen (Dukes C)
Gastrointestinal	cancer antigen CA242
Gastrointestinal	soluble <i>erb</i> -B-2
Gastrointestinal	cancer antigen CA195

Gastrointestinal Gastrointestinal TPS Esophageal CYFRA 21-1 Esophageal TPA Esophageal TPS Esophageal TPS Esophageal Cancer antigen CA19-9 Gastric Cancer CEA Gastric Cancer Cancer antigen CA19-9 Gastric Cancer Cancer antigen CA19-9 Gastric Cancer Cancer antigen CA19-9 Lung CEA Lung CYFRA 21-1 Lung CYFRA 21-1 Lung Cancer antigen CA 125 Lung TPA Lung Cancer antigen CA 125 Pancreatic cancer Ca19-9 Pancreatic cancer Ca19-9 Pancreatic cancer Ca119 Pancreatic cancer CEA Pancreatic cancer CEA Pancreatic cancer CEA Pancreatic cancer	0	
Gastrointestinal Esophageal CYFRA 21-1 Esophageal TPA Esophageal TPS Esophageal TPS Esophageal Cancer antigen CA19-9 Gastric Cancer CEA Gastric Cancer Cancer antigen CA72-4 Lung CEA Lung CEA Lung CYFRA 21-1 Lung CYFRA 21-1 Lung Cancer antigen CA 125 Lung TPA Lung CYFRA 21-1 Cancer antigen CA 125  Lung CYFRA 21-1 Cancer antigen CA 125  Lung CYFRA 21-1 Cancer antigen CA 125  Lung CYFRA 21-1 Cancer antigen CA 125  Lung CYFRA 21-1 Cancer antigen CA 125  Lung CYFRA 21-1 Cancer antigen CA 125  CYFRA 21-1 Cancer antigen CA 125  CYFRA 21-1 Cancer antigen CA 125  CYFRA 21-1 Cancer antigen CA 125  CYFRA 21-1 CANCER ANTIGEN CA 125  CYFRA 21-1 CANCER ANTIGEN CA 125  CANCER ANTIGEN CA 125  CANCER ANTIGEN CANCER CA 125  Pancreatic cancer ca19-9 Pancreatic cancer ca119 Pancreatic cancer ca125  Pancreatic cancer CEA Pancreatic cancer	Gastrointestinal	TPA
Esophageal TPA  Esophageal TPS  Esophageal Cancer antigen CA19-9  Gastric Cancer CEA  Gastric Cancer cancer antigen CA72-4  Lung neruon specific enolase (NSE)  Lung CYFRA 21-1  Lung CYFRA 21-1  Lung squamous cell carcinoma antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca19-9  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer CEA  Pancreatic cancer CEA  Pancreatic cancer CEA	Gastrointestinal	YKL-40
Esophageal TPS  Esophageal Cancer antigen CA19-9  Gastric Cancer CEA  Gastric Cancer cancer antigen CA72-4  Lung neruon specific enolase (NSE)  Lung CYFRA 21-1  Lung cancer antigen CA 125  Lung squamous cell carcinoma antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca19  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer CEA  Pancreatic cancer CEA  Pancreatic cancer CEA	Gastrointestinal	TPS
Esophageal TPS  Esophageal cancer antigen CA19-9  Gastric Cancer CEA  Gastric Cancer cancer antigen CA72-4  Lung neruon specific enolase (NSE)  Lung CYFRA 21-1  Lung cancer antigen CA 125  Lung squamous cell carcinoma antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca119  Pancreatic cancer CEA  Pancreatic cancer CEA  Pancreatic cancer CEA  Pancreatic cancer CEA	Esophageal	CYFRA 21-1
Esophageal cancer antigen CA19-9  Gastric Cancer CEA  Gastric Cancer cancer antigen CA19-9  Gastric Cancer cancer antigen CA72-4  Lung neruon specific enolase (NSE)  Lung CEA  \Lung CYFRA 21-1  Lung cancer antigen CA 125  Lung TPA  Lung squamous cell carcinoma antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca119  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer CEA	Esophageal	TPA
Gastric Cancer CEA  Gastric Cancer cancer antigen CA19-9  Gastric Cancer cancer antigen CA72-4  Lung neruon specific enolase (NSE)  Lung CEA  \Lung CYFRA 21-1  Lung cancer antigen CA 125  Lung TPA  Lung squamous cell carcinoma antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca19-9  Pancreatic cancer ca119  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer CEA	Esophageal	TPS
Gastric Cancer cancer antigen CA19-9  Gastric Cancer cancer antigen CA72-4  Lung neruon specific enolase (NSE)  Lung CYFRA 21-1  Lung cancer antigen CA 125  Lung TPA  Lung squamous cell carcinoma antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca19  Pancreatic cancer ca119  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer CEA	Esophageal	cancer antigen CA19-9
Gastric Cancer cancer antigen CA72-4  Lung neruon specific enolase (NSE)  Lung CEA  \Lung CYFRA 21-1  Lung cancer antigen CA 125  Lung TPA  Lung squamous cell carcinoma antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca50  Pancreatic cancer ca119  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer CEA	Gastric Cancer	CEA
Lung CEA  \Lung CYFRA 21-1  Lung Cancer antigen CA 125  Lung TPA  Lung squamous cell carcinoma antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca119  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer CEA	Gastric Cancer	cancer antigen CA19-9
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Lung CYFRA 21-1  Lung Cancer antigen CA 125  Lung TPA  Lung squamous cell carcinoma antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca50  Pancreatic cancer ca119  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer	Lung	neruon specific enolase (NSE)
Lung Cancer antigen CA 125  Lung TPA  Lung squamous cell carcinoma antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca50  Pancreatic cancer ca119  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer	Lung	CEA
Lung TPA  Lung squamous cell carcinoma antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca50  Pancreatic cancer ca119  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer	\Lung	CYFRA 21-1
Lung squamous cell carcinoma antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca50  Pancreatic cancer ca119  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer	Lung	cancer antigen CA 125
antigen (SCC)  Pancreatic cancer ca19-9  Pancreatic cancer ca50  Pancreatic cancer ca119  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer	Lung	TPA
Pancreatic cancer ca19-9  Pancreatic cancer ca50  Pancreatic cancer ca119  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer	Lung	squamous cell carcinoma
Pancreatic cancer ca50  Pancreatic cancer ca119  Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer		antigen (SCC)
Pancreatic cancer call9  Pancreatic cancer cal25  Pancreatic cancer CEA  Pancreatic cancer	Pancreatic cancer	ca19-9
Pancreatic cancer ca125  Pancreatic cancer CEA  Pancreatic cancer	Pancreatic cancer	ca50
Pancreatic cancer CEA Pancreatic cancer	Pancreatic cancer	ca119
Pancreatic cancer	Pancreatic cancer	ca125
	Pancreatic cancer	CEA
Renal Cancer CD44v6	Pancreatic cancer	
55110	Renal Cancer	CD44v6
Renal Cancer E-cadherin	Renal Cancer	E-cadherin
Renal Cancer PCNA (proliferating cell	Renal Cancer	PCNA (proliferating cell
nuclear antigen)		nuclear antigen)

# **Examples**

### Germ Cell Cancers

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Non-limiting examples of tumor markers useful in the present invention for the detection of germ cell cancers include, but are not limited to, a-fetoprotein (AFP), human chorionic gonadotrophin (hCG) and its beta subunit (hCGb), lactate dehydrogenase (LDH), and placental alkaline phosphatase (PLAP).

AFP has an upper reference limit of approximately -10 kU/L after the first year of life and may be elevated in germ cell tumors, hepatocellular carcinoma and also in gastric, colon, biliary, pancreatic and lung cancers. AFP serum half life is approximately five days after orchidectomy. According to EGTM recommendations, AFP serum levels less than 1,000 kU/L correlate with a good prognosis, AFP levels between 1,000 and 10,000 kU/L, inclusive, correlate with intermediate prognosis, and AFP levels greater than 10,000 U/L correlate with a poor prognosis.

HCG is synthesized in the placenta and is also 20 produced by malignant cells. Serum hCG concentrations may be increased in pancreatic adenocarcinomas, islet cell tumors, tumors of the small and large bowel, hepatoma, stomach, lung, ovaries, breast and kidney. Because some tumors only hCGb, measurement of both hCG 25 and hCGb is recommended. Normally, serum hCG in men and pre-menopausal women is as high as -5 U/L while postmenopausal women have levels up to -10 U/L. Serum half life of hCG ranges from 16-24 hours. According to the EGTM, hCG serum levels under 5000 U/L correlate with a 30 good prognosis, levels between 5000 and 50000 U/L, inclusively correlate with an intermediate prognosis,

and hCG serum levels greater than 50000 U/L correlate with a poor prognosis. Further, normal hCG half lives correlate with good prognosis while prolonged half lives correlate with poor prognosis.

5 LDH is an enzyme expressed in cardiac and skeletal muscle as well as in other organs. The LDH-1 isoenzyme is most commonly found in testicular germ cell tumors but can also occur in a variety of benign conditions such as skeletal muscle disease and myocardial 10 infarction. Total LDH is used to measure independent prognostic value in patients with advanced germ cell tumors. LDH levels less than 1.5 x the reference range are associated with a good prognosis, levels between 1.5 and 10 x the reference range, inclusive, are associated 15 with an intermediate prognosis, and levels more than 10 x the reference range are associated with a poor prognosis.

PLAP is a enzyme of alkaline phosphatase normally expressed by placental syncytiotrophoblasts. Elevated serum concentrations of PLAP are found in seminomas, non-seminomatous tumors, and ovarian tumors, and may also provide a marker for testicular tumors. PLAP has a normal half life after surgical resection of between 0.6 and 2.8 days.

# 25 <u>Prostate Cancer</u>

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A nonlimiting example of a tumor marker useful in the present invention for the detection of prostate cancer is prostate specific antigen (PSA). PSA is a glycoprotein that is almost exclusively produced in the prostate. In human serum, uncomplexed f-PSA and a complex of f-PSA with al-anthichymotrypsin make up total

PSA (t-PSA). T-PSA is useful in determining prognosis in patients that are not currently undergoing anti-androgen treatment. Rising t-PSA levels via serial measurement indicate the presence of residual disease.

# 5 Breast Cancer

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Non-limiting examples of serum tumor markers useful in the present invention for the detection of breast cancer include, but is not limited to carcinoembryonic antigen (CEA) and MUC-1 (CA 15.3). Serum CEA and CA15.3 levels are elevated in patients with node involvement compared to patients without node involvement, and in patients with larger tumors compared to smaller tumors. Normal range cutoff points (upper limit) are 5-10 mg/L for CEA and 35-60 u/ml for CA15.3. Additional specificity (99.3%) is gained by confirming serum levels with two serial increases of more than 15%.

# Ovarian Cancer

A non-limiting example of a tumor marker useful in the present invention for the detection of ovarian cancer is CA125. Normally, women have serum CA125 levels between 0-35 kU/L; 99% of post-menopausal women have levels below 20 kU/L. Serum concentration of CA125 after chemotherapy is a strong predictor of outcome as elevated CA125 levels are found in roughly 80% of all patients with epithelial ovarian cancer. Further, prolonged CA125 half-life or a less than 7-fold decrease during early treatment is also a predictor of poor disease prognosis.

#### <u>Gastrointestinal</u> Cancers

A non-limiting example of a tumor marker useful in the present invention for the detection of colon cancer

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is carcinoembryonic antigen (CEA). CEA is a glycoprotein produced during embryonal and fetal development and has a high sensitivity for advanced carcinomas including those of the colon, breast, stomach and lung. High preor postoperative concentrations (>2.5 ng/ml) of CEA are associated with worse prognosis than are low concentrations. Further, some studies in the literature report that slow rising CEA levels indicates local recurrence while rapidly increasing levels suggests hepatic metastasis.

# Lung Cancer

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Examples of serum markers useful in the present invention to monitor lung cancer therapy include, but are not limited to, CEA, cytokeratin 19 fragments (CYFRA 21-1), and Neuron Specific Enolase (NSE).

NSE is a glycolytic isoenzyme of enolase produced in central and peripheral neurons and malignant tumors of neuroectodermal origin. At diagnosis, NSE concentrations greater than 25 ng/mL are suggestive of malignancy and lung cancer while concentrations greater than 100 ng/mL are suggestive of small cell lung cancer.

CYFRA 21-1 is a tumor marker test which uses two specific monoclonal antibodies against a cytokeratin 19 fragment. At diagnosis, CYFRA 21-1 concentrations greater than 10 ng/mL are suggestive of malignancy while concentrations greater than 30 ng/mL are suggestive of lung cancer.

Accordingly, dosing of the cyclooxygenase-2 inhibitor, matrix metalloproteinase inhibitor, and antineoplastic agent may be determined and adjusted based on measurement of tumor markers in body fluids or

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tissues, particularly based on tumor markers in serum. For example, a decrease in serum marker level relative to baseline serum marker prior to administration of the matrix metalloproteinase inhibitor, cyclooxygenase-2 inhibitor and antineoplastic agent indicates a decrease in cancer-associated changes and provides a correlation with inhibition of the cancer. In one embodiment, therefore, the method of the present invention comprises administering the cyclooxygenase-2 inhibitor, matrix metalloproteinase inhibitor, and antineoplastic agent at doses that in combination result in a decrease in one or more tumor markers, particularly a decrease in one or more serum tumor markers, in the mammal relative to baseline tumor marker levels.

Similarly, the rate of postoperative decrease of a particular marker predicts patient outcome. Decreasing tumor marker concentrations and half lives after surgery indicates a good prognosis, while tumor marker concentrations which decline slowly and don't reach the normal reference range predict residual tumor and poor prognosis. Further, during follow-up therapy, increases in tumor marker concentration predicts recurrent disease many months before clinical manifestation.

In addition to the above examples, Table No. 4,
25 below, lists several references, hereby individually
incorporated by reference herein, that describes tumor
markers and their use in detecting and monitoring tumor
growth and progression.

30 Table No. 4. Tumor marker references.

European Group on Tumor Markers Publications

Committee. Consensus Recommendations. Anticancer Research 19: 2785-2820 (1999)

Human Cytogenetic Cancer Markers. Sandra R. Wolman and Stewart Sell (eds.). Totowa, New Jersey: Humana Press. 1997

Cellular Markers of Cancer. Carleton Garrett and Stewart Sell (eds.). Totowa, New Jersey: Human Press. 1995

# Combinations with Other Treatments

The COX- 2 inhibitors and MMP inhibitors of the present invention may be used in conjunction with other treatment modalities, including, but not limited to surgery and radiation, hormonal therapy, chemotherapy, immunotherapy, and cryotherapy. The present invention may be used in conjunction with any current or future therapy.

The following discussion highlights some agents in this respect, which are illustrative, not limitative. A wide variety of other effective agents also may be used.

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# Surgery and Radiation

In general, surgery and radiation therapy are employed as potentially curative therapies for patients under 70 years of age who present with clinically localized disease and are expected to live at least 10 years.

For example, approximately 70% of newly diagnosed prostate cancer patients fall into this category. Approximately 90% of these patients (65% of total 10 patients) undergo surgery, while approximately 10% of these patients (7% of total patients) undergo radiation therapy. Histopathological examination of surgical specimens reveals that approximately 63% of patients undergoing surgery (40% of total patients) have locally 15 extensive tumors or regional (lymph node) metastasis that was undetected at initial diagnosis. These patients are at a significantly greater risk of recurrence. Approximately 40% of these patients will actually develop recurrence within five years after surgery. 20 Results after radiation are even less encouraging. Approximately 80% of patients who have undergone radiation as their primary therapy have disease persistence or develop recurrence or metastasis within five years after treatment. Currently, most of these 25 surgical and radiotherapy patients generally do not receive any immediate follow-up therapy. Rather, for example, they are monitored frequently for elevated Prostate Specific Antigen ("PSA"), which is the primary indicator of recurrence or metastasis prostate cancer.

Thus, there is considerable opportunity to use the present invention in conjunction with surgical intervention.

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# Hormonal Therapy

Hormonal ablation is the most effective palliative treatment for the 10% of patients presenting with metastatic prostate cancer at initial diagnosis.

Hormonal ablation by medication and/or orchiectomy is used to block hormones that support the further growth and metastasis of prostate cancer. With time, both the primary and metastatic tumors of virtually all of these patients become hormone-independent and resistant to therapy. Approximately 50% of patients presenting with metastatic disease die within three years after initial diagnosis, and 75% of such patients die within five years after diagnosis. Continuous supplementation with NAALADase inhibitor based drugs are used to prevent or reverse this potentially metastasis-permissive state.

Among hormones which may be used in combination with the present inventive compounds, diethylstilbestrol (DES), leuprolide, flutamide, cyproterone acetate, ketoconazole and amino glutethimide are preferred.

#### <u>Immunotherapy</u>

The COX-2 inhibitors and MMP inhibitors of the present invention may also be used in combination with monoclonal antibodies in treating cancer. For example monoclonal antibodies may be used in treating prostate cancer. A specific example of such an antibody includes cell membrane-specific anti-prostate antibody.

The present invention may also be used with

immunotherapies based on polyclonal or monoclonal
antibody-derived reagents, for instance. Monoclonal
antibody-based reagents are most preferred in this

regard. Such reagents are well known to persons of ordinary skill in the art. Radiolabelled monoclonal antibodies for cancer therapy, such as the recently approved use of monoclonal antibody conjugated with strontium-89, also are well known to persons of ordinary skill in the art.

# Antiangiogenic Therapy

The COX-2 inhibitors and MMP inhibitors may also be used in combination with other antiangiogenic agenst in treating cancer. Antiangiogenic agents include but are not limited to MMP inhibitors, integrin antagonists, angiostatin, endostatin, thrombospondin-1, and interferon alpha. Examples of preferred antiangiogenic agents include, but are not limited to vitaxin, marimastat, Bay-12-9566, AG-3340, metastat, celecoxib, rofecoxib, JTE-522, EMD-121974, and D-2163 (BMS-275291).

# Cryotherapy

- 20 Cryotherapy recently has been applied to the treatment of some cancers. Methods and compositions of the present invention also could be used in conjunction with an effective therapy of this type.
- All of the various cell types of the body can be transformed into benign or malignant neoplasia or tumor cells and are contemplated as objects of the invention.

  A "benign" tumor cell denotes the non-invasive and non-metastasized state of a neoplasm. In man the most frequent neoplasia site is lung, followed by colorectal, breast, prostate, bladder, pancreas, and then ovary.

  Other prevalent types of cancer include leukemia,

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central nervous system cancers, including brain cancer, melanoma, lymphoma, erythroleukemia, uterine cancer, and head and neck cancer. Examples 1 through 9 are provided to illustrate contemplated therapeutic combinations, and are not intended to limit the scope of the invention.

#### Illustrations

The following non-limiting illustrative examples describe various cancer diseases and therapeutic

10 approaches that may be used in the present invention, and are for illustrative purposes only. Preferred antiangiogenic agents of the below non-limiting illustrations are MMP inhibitors and COX-2 inhibitors. More preferably the MMP inhibitors include Compound M1,

15 Compound M2, Compound M3, Compound M4, Compound M5, Compound M6, Compound M7, Compound M8, Marimastat, Bay-12-9566, AG-3340, Metastat, and D-2163 (BMS-275291) and the COX-2 inhibitors include celecoxib, rofecoxib and JTE-522.

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# Example 1

#### Lung Cancer

In many countries including Japan, Europe and

America, the number of patients with lung cancer is
fairly large and continues to increase year after year
and is the most frequent cause of cancer death in both
men and women. Although there are many potential causes
for lung cancer, tobacco use, and particularly cigarette

smoking, is the most important. Additionally, etiologic
factors such as exposure to asbestos, especially in
smokers, or radon are contributory factors. Also

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occupational hazards such as exposure to uranium have been identified as an important factor. Finally, genetic factors have also been identified as another factor that increase the risk of cancer.

Lung cancers can be histologically classified into non-small cell lung cancers (e.g. squamous cell carcinoma (epidermoid), adenocarcinoma, large cell carcinoma (large cell anaplastic), etc.) and small cell lung cancer (oat cell). Non-small cell lung cancer (NSCLC) has different biological properties and responses to chemotherapeutics from those of small cell lung cancer (SCLC). Thus, chemotherapeutic formulas and radiation therapy are different between these two types of lung cancer.

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# Non-Small Cell Lung Cancer

Where the location of the non-small cell lung cancer tumor can be easily excised (stage I and II disease) surgery is the first line of therapy and offers a relatively good chance for a cure. However, in more advanced disease (stage IIIa and greater), where the tumor has extended to tissue beyond the bronchopulmonary lymph nodes, surgery may not lead to complete excision of the tumor. In such cases, the patient's chance for a cure by surgery alone is greatly diminished. Where surgery will not provide complete removal of the NSCLC tumor, other types of therapies must be utilized.

Today radiation therapy is the standard treatment to control unresectable or inoperable NSCLC. Improved results have been seen when radiation therapy has been combined with chemotherapy, but gains have been modest

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and the search continues for improved methods of combining modalities.

Radiation therapy is based on the principle that high-dose radiation delivered to a target area will result in the death of reproductive cells in both tumor and normal tissues. The radiation dosage regimen is generally defined in terms of radiation absorbed dose (rad), time and fractionation, and must be carefully defined by the oncologist. The amount of radiation a patient receives will depend on various consideration but the two most important considerations are the location of the tumor in relation to other critical structures or organs of the body, and the extent to which the tumor has spread. A prefered course of treatment for a patient undergoing radiation therapy for NSCLC will be a treatment schedule over a 5 to 6 week period, with a total dose of 50 to 60 Gy administered to the patient in a single daily fraction of 1.8 to 2.0 Gy, 5 days a week. A Gy is an abbreviation for Gray and refers to 100 rad of dose.

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However, as NSCLC is a systemic disease, and radiation therapy is a local modality, radiation therapy as a single line of therapy is unlikely to provide a cure for NSCLC, at least for those tumors that have metastasized distantly outside the zone of treatment. Thus, the use of radiation therapy with other modality regimens have important beneficial effects for the treatment of NSCLC.

Generally, radiation therapy has been combined

temporally with chemotherapy to improve the outcome of treatment. There are various terms to describe the temporal relationship of administering radiation therapy

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in combination with MMP inhibitors and COX-2 inhibitors and/or chemotherapy, and the following examples are the preferred treatment regimens and are provided for illustration only and are not intended to limit the use of other combinations. "Sequential" therapy refers to the administration of chemotherapy and/or MMP inhibitors and/or COX-2 inhibitors and/or radiation therapy separately in time in order to allow the separate administration of either chemotherapy and/or MMP inhibitors and/or COX-2 inhibitors, and/or radiation 10 therapy. "Concomitant" therapy refers to the administration of chemotherapy and/or MMP inhibitors, and/or COX-2 inhibitors and/or radiation therapy on the same day. Finally, "alternating therapy" refers to the administration of radiation therapy on the days in which 15 chemotherapy and/or MMP inhibitors and/or COX-2 inhibitors would not have been administered if it was given alone.

It is reported that advanced non-small cell lung cancers do not respond favorably to single-agent chemotherapy and useful therapies for advanced inoperable cancers have been limited. (Journal of Clinical Oncology, vol. 10, pp. 829-838 (1992)).

Japanese Patent Kokai 5-163293 refers to some

specified antibiotics of 16-membered-ring macrolides as a drug delivery carrier capable of transporting anthoracycline-type anticancer drugs into the lungs for the treatment of lung cancers. However, the macrolide antibiotics specified herein are disclosed to be only a drug carrier, and there is no reference to the therapeutic use of macrolides against non-small cell lung cancers.

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WO 93/18,652 refers to the effectiveness of the specified 16-membered-ring macrolides such as bafilomycin, etc. in treating non-small cell lung cancers, but they have not yet been clinically practicable.

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Pharmacology, vol. 41, pp. 177-183 (1990) describes that a long-term use of erythromycin increases productions of interleukins 1, 2 and 4, all of which contribute to host immune responses, but there is no reference to the effect of this drug on non-small cell lung cancers.

Teratogenesis, Carcinogenesis, and Mutagenesis, vol. 10, pp. 477-501 (1990) describes that some of antimicrobial drugs can be used as an anticancer agent, but does not refer to their application to non-small cell lung cancers.

In addition, interleukins are known to have an antitumor effect, but have not been reported to be effective against non-small cell lung cancers.

Any 14 - or 15-membered-ring macrolides have not been reported to be effective against non-small cell lung cancers.

However, several chemotherapeutic agents have been shown to be efficacious against NSCLC. Preferred

25 chemotherapeutic agents that can be used in the present invention against NSCLC include etoposide, carboplatin, methotrexate, 5-Fluorouracil, epirubicin, doxorubicin, taxol, inhibitor of normal mitotic activity; and cyclophosphamide. Even more preferred chemotherapeutic agents active against NSCLC include cisplatin, ifosfamide, mitomycin C, epirubicin, vinblastine, and vindesine.

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Other agents that are under investigation for use against NSCLC include: camptothecins, a topoisomerase 1 inhibitor; navelbine (vinorelbine), a microtubule assebly inhibitor; gemcitabine, a deoxycytidine analogue; fotemustine, a nitrosourea compound; and edatrexate, a antifol.

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The overall and complete response rates for NSCLC has been shown to increase with use of combination chemotherapy as compared to single-agent treatment. Haskel CM: Chest. 99: 1325, 1991; Bakowski MT: Cancer Treat Rev 10:159, 1983; Joss RA: Cancer Treat Rev 11:205, 1984.

A preferred therapy for the treatment of NSCLC is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in 15 combination with the following combinations of antineoplastic agents: 1) itosfamide, cisplatin, etoposide; 2) cyclophoshamide, doxorubicin, cisplatin; 3) isofamide, carboplatin, etoposide; 4) bleomycin, 20 etoposide, cisplatin; 5) isofamide, mitomycin, cisplatin; 6) cisplatin, vinblastine; 7) cisplatin, vindesine; 8) mitomycin C, vinblastine, cisplatin; 9) mitomycin C, vindesine, cisplatin; 10) isofamide, etoposide; 11) etoposide, cisplatin; 12) isofamide, mitomycin C; 13) flurouracil, cisplatin, vinblastine; 25 14) carboplatin, etoposide; or radiation therapy.

Accordingly, apart from the conventional concept of anticancer therapy, there is a strong need for the development of therapies practicably effective for the treatment of non-small cell lung cancers.

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esorubicin.

### Small Cell Lung Cancer

Approximately 15 to 20 percent of all cases of lung cancer reported worldwide is small cell lung cancer (SCLC). Inde DC: Cancer 54:2722, 1984. Currently, treatment of SCLC incorporates multi-modal therapy, including chemotherapy, radiation therapy and surgery. Response rates of localized or disseminated SCLC remain high to systemic chemotherapy, however, persistence of the primary tumor and persistence of the tumor in the associated lymph nodes has led to the integration of several therapeutic modalities in the treatment of SCLC.

A preferred therapy for the treatment of lung cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 15 inhibitors in combination with the following antineoplastic agents: vincristine, cisplatin, carboplatin, cyclophosphamide, epirubicin (high dose), etoposide (VP-16) I.V., etoposide (VP-16) oral, isofamide, teniposide (VM-26), and doxorubicin. Other 20 preferred single-agents chemotherapeutic agents that may be used in the present invention include BCNU (carmustine), vindesine, hexamethylmelamine (altretamine), methotrexate, nitrogen mustard, and CCNU (lomustine). Other chemotherapeutic agents under 25 investigation that have shown activity againe SCLC include iroplatin, gemcitabine, lonidamine, and taxol. Single-agent chemotherapeutic agents that have not shown activity against SCLC include mitoguazone, mitomycin C, aclarubicin, diaziquone, bisantrene, cytarabine, 30 idarubicin, mitomxantrone, vinblastine, PCNU and

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The poor results reported from single-agent chemotherapy has led to use of combination chemotherapy.

A preferred therapy for the treatment of NSCLC is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: 1) etoposide (VP-16), cisplatin; 2) cyclophosphamide, adrianmycin [(doxorubicin), vincristine, etoposide (VP-16)]; 3) Cyclophosphamide, adrianmycin(doxorubicin), vincristine; 4) Etoposide (VP-16), ifosfamide, cisplatin; 5) etoposide (VP-16), carboplatin; 6) cisplatin, vincristine (Oncovin), doxorubicin, etoposide.

Additionally, radiation therapy in conjunction with the preferred combinations of COX-2 inhibitors and MMP inhibitors and systemic chemotherapy is contemplated to be effective at increasing the response rate for SCLC patients. The typical dosage regimen for radiation therapy ranges from 40 to 55 Gy, in 15 to 30 fractions, 3 to 7 times week. The tissue volume to be irradiated is determined by several factors and generally the hilum and subcarnial nodes, and bialteral mdiastinal nodes up to the thoraic inlet are treated, as well as the primary tumor up to 1.5 to 2.0 cm of the margins.

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### Example 2

# Colorectal Cancer

Survival from colorectal cancer depends on the

30 stage and grade of the tumor, for example precursor
adenomas to metastatic adenocarcinoma. Generally,
colorectal cancer can be treated by surgically removing

improve survival rates.

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the tumor, but overall survival rates remain between 45 and 60 percent. Colonic excision morbidity rates are fairly low and is generally associated with the anastomosis and not the extent of the removal of the tumor and local tissue. In patients with a high risk of reoccurrence, however, chemotherapy has been incorporated into the treatment regimen in order to

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Dumor metastasis prior to surgery is generally

believed to be the cause of surgical intervention
failure and up to one year of chemotherapy is required
to kill the non-excised tumor cells. As severe toxicity
is associated with the chemotherapeutic agents, only
patients at high risk of recurrence are placed on

chemotherapy following surgery. Thus, the incorporation
of an antiangiogenesis inhibitor into the management of
colorectal cancer will play an important role in the
treatment of colorectal cancer and lead to overall
improved survival rates for patients diagnosed with
colorectal cancer.

A preferred combination therapy for the treatment of colorectal cancer is surgery, followed by a regimen of one or more chemotherapeutic agents and an MMP inhibitor and a COX-2 inhibitor cycled over a one year time period. A more preferred combination therapy for the treatment of colorectal cancer is a regimen of one or more MMP inhibitors and/or COX-2 inhibitors, followed by surgical removal of the tumor from the colon or rectum and then followed be a regimen of one or more chemotherapeutic agents and one or more antiangiogenic agents, cycled over a one year time period. An even more preferred therapy for the treatment of colon cancer is a

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combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors.

A more preferred therapy for the treatment of colon cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following antineoplastic agents: fluorouracil, and Levamisole. Preferably, fluorouracil and Levamisole are used in combination.

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#### Example 3

# Breast Cancer

Today, among women in the United States, breast

15 cancer remains the most frequent diagnosed cancer. One
in 8 women in the United States are at risk of
developing breast cancer in their lifetime. Age, family
history, diet, and genetic factors have been identified
as risk factors for breast cancer. Breast cancer is the
20 second leading cause of death among women.

Different chemotherapeutic agents are known in art for treating breast cancer. Cytoxic agents used for treating breast cancer include doxorubicin, cyclophosphamide, methotrexate, 5-

fluorouracil, mitomycin C, mitoxantrone, taxol, and epirubicin. CANCER SURVEYS, Breast Cancer volume 18, Cold Spring Harbor Laboratory Press, 1993.

In the treatment of locally advanced noninflammatory breast cancer, MMP inhibitors and/or COX-2 inhibitors can be used to treat the disease in combination with other COX-2 inhibitors, other MMP inhibitors, antiangiogenic agents, or in combination

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with surgery, radiation therapy or with chemotherapeutic agents. Preferred combinations of chemotherapeutic agents, radiation therapy and surgery that can be used in combination with the present invention include, but are not limited to the following combinations: 1) doxorubicin, vincristine, radical mastectomy; 2) doxorubicin, vincristine, radiation therapy; 3) cyclophosphamide, doxorubicin, 5-flourouracil, vincristine, prednisone, mastecomy; 4) cyclophosphamide, 10 doxorubicin, 5-flourouracil, vincristine, prednisone, radiation therapy; 5) cyclophosphamide, doxorubicin, 5flourouracil, premarin, tamoxifen, radiation therapy for pathologic complete response; 6) cyclophosphamide, doxorubicin, 5-flourouracil, premarin, tamoxifen, 15 mastectomy, radiation therapy for pathologic partial response; 7) mastectomy, radiation therapy, levamisole; 8) mastectomy, radiation therapy; 9) mastectomy, vincristine, doxorubicin, cyclophosphamide, levamisole; 10) mastectomy, vincristine, doxorubicin, cyclophosphamide; 11) mastecomy, cyclophosphamide, 20 doxorubicin, 5-fluorouracil, tamoxifen, halotestin, radiation therapy; 12) mastecomy, cyclophosphamide,

In the treatment of locally advanced inflammatory

breast cancer, MMP inhibitors and/or COX-2 inhibitors

can be used to treat the disease in combination with

other MMP inhibitors and/or COX-2 inhibitors,

antiangiogenic agents, or in combination with surgery,

radiation therapy or with chemotherapeutic agents.

Preferred combinations of chemotherapeutic agents,

radiation therapy and surgery that can be used in

combination with the present invention include, but or

doxorubicin, 5-fluorouracil, tamoxifen, halotestin.

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not limited to the following combinations: 1) cyclophosphamide, doxorubicin, 5-fluorouracil, radiation therapy; 2) cyclophosphamide, doxorubicin, 5fluorouracil, mastectomy, radiation therapy; 3) 5flurouracil, doxorubicin, clyclophosphamide, vincristine, prednisone, mastectomy, radiation therapy; 4) 5-flurouracil, doxorubicin, clyclophosphamide, vincristine, mastectomy, radiation therapy; 5) cyclophosphamide, doxorubicin, 5-fluorouracil, vincristine, radiation therapy; 6) cyclophosphamide, 10 doxorubicin, 5-fluorouracil, vincristine, mastectomy, radiation therapy; 7) doxorubicin, vincristine, methotrexate, radiation therapy, followed by vincristine, cyclophosphamide, 5-florouracil; 8) doxorubicin, vincristine, cyclophosphamide, 15 methotrexate, 5-florouracil, radiation therapy, followed by vincristine, cyclophosphamide, 5-florouracil; 9) surgery, followed by cyclophosphamide, methotrexate, 5fluorouracil, predinsone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, 20 methotrexate, 5-fluorouracil, predinsone, tamoxifen, doxorubicin, vincristine, tamoxifen; 10) surgery, followed by cyclophosphamide, methotrexate, 5fluorouracil, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, 25 predinsone, tamoxifen, doxorubicin, vincristine, tamoxifen; 11) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, 30 doxorubicin, vincristine, tamoxifen;; 12) surgery,

followed by cyclophosphamide, methotrexate, 5-

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fluorouracil, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, doxorubicin, vincristine; 13) surgery, followed by cyclophosphamide, methotrexate, 5-5 fluorouracil, predinsone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, doxorubicin, vincristine, tamoxifen; 14) surgery, followed by cyclophosphamide, methotrexate, 5fluorouracil, followed by radiation therapy, followed by 10 cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, doxorubicin, vincristine; 15) surgery, followed by cyclophosphamide, methotrexate, 5fluorouracil, predinsone, tamoxifen, followed by 15 radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, vincristine; 16) 5-florouracil, doxorubicin, cyclophosphamide followed by mastectomy, followed by 5-florouracil, doxorubicin, cyclophosphamide, followed by radtiation 20 therapy.

In the treatment of metastatic breast cancer, MMP inhibitors and/or COX-2 inhibitors can be used to treat the disease in combination with other MMP inhibitors and/or COX-2 inhibitors, antiangiogenic agents, or in combination with surgery, radiation therapy or with chemotherapeutic agents. Preferred combinations of chemotherapeutic agents that can be used in combination with the angiogenesis inhibitors of the present invention include, but are not limited to the following combinations: 1) cyclosphosphamide, methotrexate, 5-fluorouracil; 2) cyclosphosphamide, adriamycin, 5-fluorouracil; 3) cyclosphosphamide, methotrexate, 5-fluorouracil; 3) cyclosphosphamide, methotrexate, 5-

flurouracil, vincristine, prednisone; 4) adriamycin, vincristine; 5) thiotepa, adriamycin, vinblastine; 6) mitomycin, vinblastine; 7) cisplatin, etoposide.

# 5 Example 4

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# Prostate Cancer

Prostate cancer is now the leading form of cancer among men and the second most frequent cause of death from cancer in men. It is estimated that more than 165,000 new cases of prostate cancer were diagnosed in 1993, and more than 35,000 men died from prostate cancer in that year. Additionally, the incidence of prostate cancer has increased by 50% since 1981, and mortality from this disease has continued to increase. Previously, most men died of other illnesses or diseases before dying from their prostate cancer. We now face increasing morbidity from prostate cancer as men live longer and the disease has the opportunity to progress.

20 Current therapies for prostate cancer focus exclusively upon reducing levels of dihydrotestosterone to decrease or prevent growth of prostate cancer. In addition to the use of digital rectal examination and transrectal ultrasonography, prostate-specific antigen 25 (PSA) concentration is frequently used in the diagnosis of prostate cancer.

A preferred therapy for the treatment of prostate cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors.

U.S. Pat. No. 4,472,382 discloses treatment of benign

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prostatic hyperplasia (BPH) with an antiandrogen and certain peptides which act as LH-RH agonists.

- U.S. Pat. No. 4,596,797 discloses aromatase inhibitors as a method of prophylaxis and/or treatment of prostatic hyperplasia.
- U.S. Pat. No. 4,760,053 describes a treatment of certain cancers which combines an LHRH agonist with an antiandrogen and/or an antiestrogen and/or at least one inhibitor of sex steroid biosynthesis.
- 10 U.S. Pat. No. 4,775,660 discloses a method of treating breast cancer with a combination therapy which may include surgical or chemical prevention of ovarian secretions and administering an antiandrogen and an antiestrogen.
- U.S. Pat. No. 4,659,695 discloses a method of treatment of prostate cancer in susceptible male animals including humans whose testicular hormonal secretions are blocked by surgical or chemical means, e.g. by use of an LHRH agonist, which comprises administering an antiandrogen, e.g. flutamide, in association with at least one inhibitor of sex steroid biosynthesis, e.g. aminoglutethimide and/or ketoconazole.

## Prostate Specific Antigen

One well known prostate cancer marker is Prostate

Specific Antigen (PSA). PSA is a protein produced by
prostate cells and is frequently present at elevated
levels in the blood of men who have prostate cancer. PSA
has been shown to correlate with tumor burden, serve as
an indicator of metastatic involvement, and provide a
parameter for following the response to surgery,
irradiation, and androgen replacement therapy in

prostate cancer patients. It should be noted that
Prostate Specific Antigen (PSA) is a completely
different protein from Prostate Specific Membrane
Antigen (PSMA). The two proteins have different
structures and functions and should not be confused
because of their similar nomenclature.

## Prostate Specific Membrane Antigen (PSMA)

specific membrane antigen (PSMA) was reported as a potential prostate carcinoma marker and hypothesized to serve as a target for imaging and cytotoxic treatment modalities for prostate cancer. Antibodies against PSMA have been described and examined clinically for diagnosis and treatment of prostate cancer. In particular, Indium-111 labelled PSMA antibodies have been described and examined for diagnosis of prostate cancer and itrium-labelled PSMA antibodies have been described and examined for the treatment of prostate cancer.

## Example 5

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## Bladder Cancer

25 The classification of bladder cancer is divided into three main classes: 1) superficial disease, 2) muscle-invasive disease, and 3) metastatic disease.

Currently, transurethral resection (TUR), or segmental resection, account for first line therapy of superficial bladder cancer, i.e., disease confined to the mucosa or the lamina propria. However, intravesical therapies are necessary, for example, for the treatment

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of high-grade tumors, carcinoma in situ, incomplete resections, recurrences, and multifocal papillary. Recurrence rates range from up to 30 to 80 percent, depending on stage of cancer.

Therapies that are currently used as intravesical 5 therapies include chemotherapy, immuontherapy, bacille Calmette-Guerin (BCG) and photodynamic therapy. main objective of intravesical therapy is twofold: to prevent recurrence in high-risk patients and to treat disease that cannot by resected. The use of 10 intravesical therapies must be balanced with its potentially toxic side effects. Additionally, BCG requires an unimpaired immune system to induce an antitumor effect. Chemotherapeutic agents that are known to be inactive against superficial bladder cancer 15 include Cisplatin, actinomycin D, 5-fluorouracil, bleomycin, and cyclophosphamide methotrxate.

In the treatment of superficial bladder cancer, MMP inhibitors and/or COX-2 inhibitors can be used to treat the disease in combination with other MMP inhibitors and/or COX-2 inhibitors, antiangiogenic agents, or in combination with surgery (TUR), chemotherapy and intravesical therapies.

A preferred therapy for the treatment of superficial bladder cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with: thiotepa (30 to 60 mg/day), mitomycin C (20 to 60 mg/day), and doxorubicin (20 to 80 mg/day).

A preferred intravesicle immunotherapeutic agent that may be used in the present invention is BCG. A preferred daily dose ranges from 60 to 120 mg, depending

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on the strain of the live attenuated tuberculosis organism used.

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A preferred photodynamic therapuetic agent that may be used with the present invention is Photofrin I, a photosensitizing agent, administered intravenously. It is taken up by the low-density lipoprotein receptors of the tumor cells and is activated by exposure to visible light. Additionally, neomydium YAG laser activation generates large amounts of cytotoxic free radicals and singlet oxygen.

In the treatment of muscle-invasive bladder cancer, MMP inhibitors and/or COX-2 inhibitors can be used to treat the disease in combination with other MMP inhibitors and/or COX-2 inhibitors, antiangiogenic agents, or in combination with surgery (TUR), intravesical chemotherapy, radiation therapy, and radical cystectomy with pelvic lymph node dissection.

A preferred radiation dose for the treatment of bladder cancer is between 5,000 to 7,000 cGY in fractions of 180 to 200 cGY to the tumor. Additionally, 3,500 to 4,700 cGY total dose is administered to the normal bladder and pelvic contents in a four-field technique. Radiation therapy should be considered only if the patient is not a surgical candidate, but may be considered as preoperative therapy.

A preferred combination of surgery and chemotherapeutic agents that can be used in combination with the MMP inhibitors and/or COX-2 inhibitors of the present invention is cystectomy in conjunction with five cycles of cisplatin (70 to 100 mg/m(square)); doxorubicin (50 to 60 mg/m(square); and cyclophosphamide (500 to 600 mg/m(square)).

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A more preferred therapy for the treatment of superficial bladder cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors.

An even more preferred combination for the treatment of superficial bladder cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: 1)

10 cisplatin, doxorubicin, cyclophosphamide; and 2) cisplatin, 5-fluorouracil. An even more preferred combination of chemotherapeutic agents that can be used in combination with radiation therapy and the , MMP inhibitors and/or COX-2 inhibitors is a combination of cisplatin, methotrexate, vinblastine.

Currently no curative therapy exists for metastatic bladder cancer. The present invention contemplates an effective treatment of bladder cancer leading to improved tumor inhibition or regression, as compared to current therapies.

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In the treatment of metastatic bladder cancer, MMP inhibitors and/or COX-2 inhibitors can be used to treat the disease in combination with other MMP inhibitors and/or COX-2 inhibitors, antiangiogenic agents, or in combination with surgery, radiation therapy or with chemotherapeutic agents.

A preferred therapy for the treatment of metastatic bladder cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors.

A more preferred combination for the treatment of metastatic bladder cancer is a combination of

therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplasitc agents: 1) cisplatin and methotrexate; 2) doxorubicin, vinblastine, cyclophoshamide, and 5-fluorouracil; 3) vinblastine, doxorubicin, cisplatin, methotrexate; 4) vinblastine, cisplatin, methotrexate; 5) cyclophosphamide, doxorubicin, cisplatin; 6) 5-fluorouracil, cisplatin.

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#### 10 Example 6

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### Pancreas Cancer

Approximately 2% of new cancer cases diagnoses in the United States is pancreatic cancer. Pancreatic cancer is generally classified into two clinical types: 1) adenocarcinoma (metastatic and non-metastatic), and 2) cystic neoplasms (serous cystadenomas, mucinous cystic neoplasms, papilary cystic neoplasms, acinar cell systadenocarcinoma, cystic choriocarcinoma, cystic teratomas, angiomatous neoplasms).

Preferred combinations of therapy for the treatment of non-metastatic adenocarcinoma that may be used in the present invention include the use of MMP inhibitors and/or COX-2 inhibitors along with preoperative bilary tract decompression (patients presenting with obstructive jaundice); surgical resection, including standard resection, extended or radial resection and distal pancreatectomy (tumors of body and tail); adjuvant radiation; and chemotherapy.

30 For the treatment of metastatic adenocarcinoma, a preferred combination therapy consists of an antiangiogenesis inhibitor of the present invention in combination with continuous treatment of 5-fluorouracil, followed by weekly cisplatin therapy.

A more preferred combination therapy for the treatment of cystic neoplasms is the use of MMP inhibitors and/or COX-2 inhibitors along with resection.

## Example 7

## Ovary Cancer

10 Celomic epithelial carcinoma accounts for approximately 90% of ovarian cancer cases. A preferred therapy for the treatment of ovary cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors.

Preferred single agents that can be used in combination with an antiangiogenesis agent include, but are not limited to: alkylating agents, ifosfamide, cisplatin, carboplatin, taxol, doxorubicin, 5-fluorouracil, methotrexate, mitomycin,

20 hexamethylmelamine, progestins, antiestrogens, prednimustine, dihydroxybusulfan, galactitol, interferon alpha, and interferon gama.

Preferred combinations for the treatment of celomic epithelial carcinoma is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; 2) hexamthylmelamine, cyclosphamide, doxorubicin, cisplatin; 3) cyclophosphamide, hexamehtylmelamine, 5-flurouracil,

cyclophosphamide, hexamehtylmelamine, 5-flurouracil, cisplatin; 4) melphalan, hexamethylmelamine, cyclophosphamide; 5) melphalan, doxorubicin,

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cyclophosphamide; 6) cyclophosphamide, cisplatin, carboplatin; 7) cyclophosphamide, doxorubicin, hexamethylmelamine, cisplatin; 8) cyclophosphamide, doxorubicin, hexamethylmelamine, carboplatin; 9) cyclophosphamide, cisplatin; 10) hexamethylmelamine, doxorubicin, carboplatin; 11) cyclophosphamide, hexamethlmelamine, doxorubicin, cisplatin; 12) carboplatin, cyclophosphamide; 13) cisplatin, cyclophosphamide.

Germ cell ovarian cancer accounts for approximately
5% of ovarian cancer cases. Germ cell ovarian
carcinomas are classified into two main groups: 1)
dysgerminoma, and nondysgerminoma. Nondysgerminoma is
further classified into teratoma, endodermal sinus
tumor, embryonal carcinoma, chloricarcinoma,
polyembryoma, and mixed cell tumors.

A preferred therapy for the treatment of germ cell carcinoma is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors.

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A more preferred therapy for the treatment of germ cell carcinoma is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: 1) vincristine, actinomycin D, cyclophosphamide; 2) bleomycin, etoposide, cisplatin; 3) vinblastine, bleomycin, cisplatin.

Cancer of the fallopian tube is the least common

type of ovarian cancer, accounting for approximately 400

new cancer cases per year in the United States.

Papillary serous adenocarcinoma accounts for

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approximately 90% of all malignancies of the ovarian tube.

A preferred therapy for the treatment of fallopian tube cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors.

A more preferred therapy for the treatment of fallopian tube cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: alkylating agents, ifosfamide, cisplatin, carboplatin, taxol, doxorubicin, 5-fluorouracil, methotrexate, mitomycin, hexamethylmelamine, progestins, antiestrogens, prednimustine, dihydroxybusulfan,

galactitol, interferon alpha, and interferon gama.

An even more preferred therapy for the treatment of fallopian tube cancer is a combination of therapeutically effective amounts of one or more MMP 20 inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; 2) hexamthylmelamine, cyclosphamide, doxorubicin, cisplatin; 3) cyclophosphamide, hexamehtylmelamine, 5-25 flurouracil, cisplatin; 4) melphalan, hexamethylmelamine, cyclophosphamide; 5) melphalan, doxorubicin, cyclophosphamide; 6) cyclophosphamide, cisplatin, carboplatin; 7) cyclophosphamide, doxorubicin, hexamethylmelamine, cisplatin; 8) 30 cyclophosphamide, doxorubicin, hexamethylmelamine, carboplatin; 9) cyclophosphamide, cisplatin; 10)

hexamethylmelamine, doxorubicin, carboplatin; 11)

cyclophosphamide, hexamethlmelamine, doxorubicin, cisplatin; 12) carboplatin, cyclophosphamide; 13) cisplatin, cyclophosphamide.

# 5 Example 8

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# Central Nervous System Cancers

Central nervous system cancer accounts for approximately 2% of new cancer cases in the United

10 States. Common intracranial neoplasms include glioma, meninigioma, neurinoma, and adenoma.

A preferred therapy for the treatment of central nervous system cancers is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors.

A preferred therapy for the treatment of maligant glioma is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following 20 combinations of therapies and antineoplastic agents: 1) radiation therapy, BCNU (carmustine); 2) radiation therapy, methyl CCNU (lomustine); 3) radiation therapy, medol; 4) radiation therapy, procarbazine; 5) radiation therapy, BCNU, medrol; 6) hyperfraction radiation 25 therapy, BCNU; 7) radiation therapy, misonidazole, BCNU; 8) radiation therapy, streptozotocin; 9) radiation therapy, BCNU, procarbazine; 10) radiation therapy, BCNU, hydroxyurea, procarbazine, VM-26; 11) radiation therapy, BNCU, 5-flourouacil; 12) radiation therapy, Methyl CCNU, dacarbazine; 13) radiation therapy,

Methyl CCNU, dacarbazine; 13) radiation therapy, misonidazole, BCNU; 14) diaziquone; 15) radiation therapy, PCNU; 16) procarbazine (matulane), CCNU,

vincristine. A preferred dose of radiation therapy is about 5,500 to about 6,000 cGY. Preferred radiosensitizers include misonidazole, intra-arterial Budr and intravenous iododeoxyuridine (IUdR). It is also contemplated that radiosurgery may be used in combinations with antiangiogenesis agents.

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# Example 9

Additional examples of combinations are listed in 10 Table No 22.

Table No. 22. Therapy Combinations

COX-2	MMP Inhibitor
Inhibitor	
Celecoxib	Compound M1
Celecoxib	Compound M2
Celecoxib	Compound M3
Celecoxib	Compound M4
Celecoxib	Compound M5
Celecoxib	Compound M7
Celecoxib	Bay-12-9566
Celecoxib	Metastat
Celecoxib	D-2163
Celecoxib	D-1927
Rofecoxib	Compound M1
Rofecoxib	Compound M2
Rofecoxib	Compound M3
Rofecoxib	Compound M4
Rofecoxib	Compound M5
Rofecoxib	Compound M7
Rofecoxib	Marimastat

Rofecoxib	Bay-12-9566
Rofecoxib	AG-3340
Rofecoxib	Metastat
Rofecoxib	D-2163
Rofecoxib	D-1927
JTE-522	Compound M1
JTE-522	Compound M2
JTE-522	Compound M3
JTE-522	Compound M4
JTE-522	Compound M5
JTE-522	Compound M7
JTE-522	Marimastat
JTE-522	Bay-12-9566
JTE-522	AG-3340
JTE-522	Metastat
JTE-522	D-2163
JTE-522	D-1927

Further additional examples of combinations are listed in Table No 23.

5 Table No. 23. Additional examples of combination therapies

COX-2	MMP	Antineoplastic	Indication
Inhibitor	Inhibitor	Agent	
Celecoxib	Compound M1	Anastrozole	Breast
Celecoxib	Compound M1	Capecitabine	Breast
Celecoxib	Compound M1	Docetaxel	Breast
Celecoxib	Compound M1	Gemcitabine	Breast,
			Pancreas
Celecoxib	Compound M1	Letrozole	Breast

Celecoxib	Compound M1	Megestrol	Breast
Celecoxib	Compound M1	Paclitaxel	Breast
Celecoxib	Compound M1	Tamoxifen	Breast
Celecoxib	Compound M1	Toremifene	Breast
Celecoxib	Compound M1	Vinorelbine	Breast,
			Lung
Celecoxib	Compound M1	Topotecan	Lung
Celecoxib	Compound M1	Etoposide	Lung
Celecoxib	Compound M1	Fluorouracil	Colon
Celecoxib	Compound M1	Irinotecan	Colon,
	•	(CPT-11)	Bladder
Celecoxib	Compound M1	Retinoids	Colon
Celecoxib	Compound M1	DFMO	Colon
Celecoxib	Compound M1	Ursodeoxycholi	Colon
		c acid	
Celecoxib	Compound M1	calcium	Colon
		carbonate	
Celecoxib	Compound M1	selenium	Colon
Celecoxib	Compound M1	sulindac	Colon
		sulfone	
Celecoxib	Compound M1	Carboplatin	Brain
Celecoxib	Compound M1	Goserelin	Prostate
		Acetate	
Celecoxib	Compound M1	Ketoconazole	Prostate
Celecoxib	Compound M1	Cisplatin	
Celecoxib	Compound M2	Anastrozole	Breast
Celecoxib	Compound M2	Capecitabine	Breast
Celecoxib	Compound M2	Docetaxel	Breast
Celecoxib	Compound M2	Gemcitabine	Breast,
			Pancreas
Celecoxib	Compound M2	Letrozole	Breast

Celecoxib	Compound M2	Megestrol	Breast
Celecoxib	Compound M2	Paclitaxel	Breast
Celecoxib	Compound M2	Tamoxifen	Breast
Celecoxib	Compound M2	Toremifene	Breast
Celecoxib	Compound M2	Vinorelbine	Breast,
			Lung
Celecoxib	Compound M2	Topotecan	Lung
Celecoxib	Compound M2	Etoposide	Lung
Celecoxib	Compound M2	Fluorouracil	Colon
Celecoxib	Compound M2	Irinotecan	Colon,
		(CPT-11)	Bladder
Celecoxib	Compound M2	Retinoids	Colon
Celecoxib	Compound M2	DFMO	Colon
Celecoxib	Compound M2	Ursodeoxycholi	Colon
		c acid	:
Celecoxib	Compound M2	calcium	Colon
		carbonate	
Celecoxib	Compound M2	selenium	Colon
Celecoxib	Compound M2	sulindac	Colon
		sulfone	
Celecoxib	Compound M2	Carboplatin	Brain
Celecoxib	Compound M2	Goserelin	Prostate
		Acetate	
Celecoxib	Compound M2	Ketoconazole	Prostate
Celecoxib	Compound M2	Cisplatin	
Celecoxib	Compound M3	Anastrozole	Breast
Celecoxib	Compound M3	Capecitabine	Breast
Celecoxib	Compound M3	Docetaxel	Breast
Celecoxib	Compound M3	Gemcitabine	Breast,
			Pancreas
Celecoxib	Compound M3	Letrozole	Breast
			<del></del>

Celecoxib	Compound M3	Megestrol	Breast
Celecoxib	Compound M3	Paclitaxel	Breast
Celecoxib	Compound M3	Tamoxifen	Breast
Celecoxib	Compound M3	Toremifene	Breast
Celecoxib	Compound M3	Vinorelbine	Breast,
			Lung
Celecoxib	Compound M3	Topotecan	Lung
Celecoxib	Compound M3	Etoposide	Lung
Celecoxib	Compound M3	Fluorouracil	Colon
Celecoxib	Compound M3	Irinotecan	Colon,
		(CPT-11)	Bladder
Celecoxib	Compound M3	Retinoids	Colon
Celecoxib	Compound M3	DFMO	Colon
Celecoxib	Compound M3	Ursodeoxycholi	Colon
		c acid	
Celecoxib	Compound M3	calcium	Colon
		carbonate	
Celecoxib	Compound M3	selenium	Colon
Celecoxib	Compound M3	sulindac	Colon
		sulfone	
Celecoxib	Compound M3	Carboplatin	Brain
Celecoxib	Compound M3	Goserelin	Prostate
		Acetate	
Celecoxib	Compound M3	Ketoconazole	Prostate
Celecoxib	Compound M3	Cisplatin	-
Celecoxib	Compound M4	Anastrozole	Breast
Celecoxib	Compound M4	Capecitabine	Breast
Celecoxib	Compound M4	Docetaxel	Breast,
			Pancreas
Celecoxib	Compound M4	Gemcitabine	Breast
Celecoxib	. Compound M4	Letrozole	Breast
F			

Celecoxib	Compound M4		Breast
Celecoxib	Compound M4	Paclitaxel	Breast
Celecoxib	Compound M4	Tamoxifen	Breast
Celecoxib	Compound M4	Toremifene	Breast,
			Lung
Celecoxib	Compound M4	Vinorelbine	Lung
Celecoxib	Compound M4	Topotecan	Lung
Celecoxib	Compound M4	Etoposide	Colon
Celecoxib	Compound M4	Fluorouracil	Colon,
			Bladder
Celecoxib	Compound M4	Irinotecan	Colon
		(CPT-11)	
Celecoxib	Compound M4	Retinoids	Colon
Celecoxib	Compound M4	DFMO	Colon
Celecoxib	Compound M4	Ursodeoxycholi	Colon
		c acid	-
Celecoxib	Compound M4	calcium	Colon
		carbonate	
Celecoxib	Compound M4	selenium	Colon
Celecoxib	Compound M4	sulindac	Colon
		sulfone	;
Celecoxib	Compound M4	Carboplatin	Brain
Celecoxib	Compound M4	Goserelin	Prostate
		Acetate	
Celecoxib	Compound M4	Ketoconazole	Prostate
Celecoxib	Compound M4	Cisplatin	
Celecoxib	Compound M5	Anastrozole	Breast
Celecoxib	Compound M5	Capecitabine	Breast
Celecoxib	Compound M5	Docetaxel	Breast,
			Pancreas
Celecoxib	Compound M5	Gemcitabine	Breast
L.,	<del></del>		

Celecoxib         Compound M5         Letrozole         Breast           Celecoxib         Compound M5         Megestrol         Breast           Celecoxib         Compound M5         Paclitaxel         Breast           Celecoxib         Compound M5         Tamoxifen         Breast           Celecoxib         Compound M5         Toremifene         Breast           Lung         Celecoxib         Compound M5         Vinorelbine         Lung           Celecoxib         Compound M5         Topotecan         Lung           Celecoxib         Compound M5         Etoposide         Colon           Celecoxib         Compound M5         Fluorouracil         Colon           Celecoxib         Compound M5         Fluorouracil         Colon           Celecoxib         Compound M5         Retinoids         Colon           Celecoxib         Compound M5         Retinoids         Colon           Celecoxib         Compound M5         DFMO         Colon           Celecoxib         Compound M5         Calcium         Colon           Celecoxib         Compound M5         selenium         Colon           Celecoxib         Compound M5         Carboplatin         Brain				
Celecoxib Compound M5 Paclitaxel Breast Celecoxib Compound M5 Tamoxifen Breast Celecoxib Compound M5 Toremifene Breast, Lung Celecoxib Compound M5 Vinorelbine Lung Celecoxib Compound M5 Topotecan Lung Celecoxib Compound M5 Etoposide Colon Celecoxib Compound M5 Fluorouracil Colon, Bladder Celecoxib Compound M5 Irinotecan Colon (CPT-11) Celecoxib Compound M5 Retinoids Colon Celecoxib Compound M5 DFMO Colon Celecoxib Compound M5 Ursodeoxycholi Colon c acid Celecoxib Compound M5 calcium Colon Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 sulindac Colon Celecoxib Compound M5 Sulindac Colon Celecoxib Compound M5 Carboplatin Brain Celecoxib Compound M5 Goserelin Prostate Celecoxib Compound M5 Ketoconazole Prostate Celecoxib Compound M5 Cisplatin Celecoxib Compound M5 Cisplatin Celecoxib Compound M5 Cisplatin Celecoxib Compound M5 Cisplatin Celecoxib Compound M5 Cisplatin Celecoxib Compound M7 Anastrozole Breast Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Letrozole	Breast
Celecoxib Compound M5 Tamoxifen Breast  Celecoxib Compound M5 Toremifene Breast,  Lung  Celecoxib Compound M5 Vinorelbine Lung  Celecoxib Compound M5 Topotecan Lung  Celecoxib Compound M5 Etoposide Colon  Celecoxib Compound M5 Fluorouracil Colon,  Bladder  Celecoxib Compound M5 Irinotecan Colon  (CPT-11)  Celecoxib Compound M5 Retinoids Colon  Celecoxib Compound M5 DFMO Colon  Celecoxib Compound M5 Ursodeoxycholi Colon  c acid  Celecoxib Compound M5 calcium Colon  c acid  Celecoxib Compound M5 selenium Colon  Celecoxib Compound M5 selenium Colon  Celecoxib Compound M5 Sulindac Colon  Celecoxib Compound M5 Carboplatin Brain  Celecoxib Compound M5 Goserelin Prostate  Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Anastrozole Breast  Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Megestrol	Breast
Celecoxib Compound M5 Toremifene Breast, Lung  Celecoxib Compound M5 Vinorelbine Lung  Celecoxib Compound M5 Topotecan Lung  Celecoxib Compound M5 Etoposide Colon  Celecoxib Compound M5 Fluorouracil Colon, Bladder  Celecoxib Compound M5 Irinotecan Colon (CPT-11)  Celecoxib Compound M5 Retinoids Colon  Celecoxib Compound M5 DFMO Colon  Celecoxib Compound M5 Ursodeoxycholi Colon  c acid  Celecoxib Compound M5 calcium Colon  carbonate  Celecoxib Compound M5 selenium Colon  Celecoxib Compound M5 sulindac Colon  Celecoxib Compound M5 Carboplatin Brain  Celecoxib Compound M5 Goserelin Prostate  Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Anastrozole Breast  Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Paclitaxel	Breast
Celecoxib Compound M5 Vinorelbine Lung  Celecoxib Compound M5 Topotecan Lung  Celecoxib Compound M5 Etoposide Colon  Celecoxib Compound M5 Fluorouracil Colon,  Bladder  Celecoxib Compound M5 Irinotecan Colon  (CPT-11)  Celecoxib Compound M5 Retinoids Colon  Celecoxib Compound M5 DFMO Colon  Celecoxib Compound M5 Ursodeoxycholi Colon  c acid  Celecoxib Compound M5 calcium Colon  carbonate  Celecoxib Compound M5 selenium Colon  Celecoxib Compound M5 selenium Colon  Celecoxib Compound M5 Selenium Colon  Celecoxib Compound M5 Selenium Prostate  Celecoxib Compound M5 Goserelin Prostate  Celecoxib Compound M5 Goserelin Prostate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Anastrozole Breast  Celecoxib Compound M7 Anastrozole Breast	Celecoxib	Compound M5	Tamoxifen	Breast
Celecoxib Compound M5 Vinorelbine Lung Celecoxib Compound M5 Topotecan Lung Celecoxib Compound M5 Etoposide Colon Celecoxib Compound M5 Fluorouracil Colon, Bladder Celecoxib Compound M5 Irinotecan Colon (CPT-11) Celecoxib Compound M5 Retinoids Colon Celecoxib Compound M5 DFMO Colon Celecoxib Compound M5 Ursodeoxycholi Colon c acid Celecoxib Compound M5 calcium Colon Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 sulindac Colon Celecoxib Compound M5 Sulindac Colon Celecoxib Compound M5 Carboplatin Brain Celecoxib Compound M5 Goserelin Prostate Celecoxib Compound M5 Goserelin Prostate Celecoxib Compound M5 Cisplatin Celecoxib Compound M5 Cisplatin Celecoxib Compound M7 Anastrozole Breast Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Toremifene	Breast,
Celecoxib Compound M5 Topotecan Lung Celecoxib Compound M5 Etoposide Colon Celecoxib Compound M5 Fluorouracil Colon, Bladder Celecoxib Compound M5 Irinotecan Colon (CPT-11) Celecoxib Compound M5 Retinoids Colon Celecoxib Compound M5 DFMO Colon Celecoxib Compound M5 Ursodeoxycholi Colon c acid Celecoxib Compound M5 calcium Colon carbonate Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 Selenium Colon Celecoxib Compound M5 Selenium Prostate Celecoxib Compound M5 Carboplatin Brain Celecoxib Compound M5 Goserelin Prostate Acetate Celecoxib Compound M5 Cisplatin Celecoxib Compound M5 Cisplatin Celecoxib Compound M7 Anastrozole Breast Celecoxib Compound M7 Anastrozole Breast			٠	Lung
Celecoxib Compound M5 Etoposide Colon  Celecoxib Compound M5 Fluorouracil Colon, Bladder  Celecoxib Compound M5 Irinotecan Colon (CPT-11)  Celecoxib Compound M5 Retinoids Colon  Celecoxib Compound M5 DFMO Colon  Celecoxib Compound M5 Ursodeoxycholi Colon  c acid  Celecoxib Compound M5 calcium Colon  carbonate  Celecoxib Compound M5 selenium Colon  Celecoxib Compound M5 sulindac Colon  Celecoxib Compound M5 Carboplatin Brain  Celecoxib Compound M5 Goserelin Prostate  Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Anastrozole Breast  Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Vinorelbine	Lung
Celecoxib Compound M5 Fluorouracil Colon, Bladder  Celecoxib Compound M5 Irinotecan Colon (CPT-11)  Celecoxib Compound M5 Retinoids Colon Celecoxib Compound M5 DFMO Colon  Celecoxib Compound M5 Ursodeoxycholi Colon c acid  Celecoxib Compound M5 calcium Colon carbonate  Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 sulindac Colon Sulfone  Celecoxib Compound M5 Carboplatin Brain Celecoxib Compound M5 Goserelin Prostate Acetate  Celecoxib Compound M5 Ketoconazole Prostate Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Capecitabine Breast  Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Topotecan	Lung
Celecoxib Compound M5 Irinotecan Colon (CPT-11)  Celecoxib Compound M5 Retinoids Colon Celecoxib Compound M5 DFMO Colon Celecoxib Compound M5 Ursodeoxycholi Colon c acid  Celecoxib Compound M5 calcium Colon carbonate  Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 sulindac Colon Sulfone  Celecoxib Compound M5 Carboplatin Brain Celecoxib Compound M5 Goserelin Prostate Acetate  Celecoxib Compound M5 Ketoconazole Prostate Celecoxib Compound M5 Cisplatin Celecoxib Compound M7 Capecitabine Breast Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Etoposide	Colon
Celecoxib Compound M5 Irinotecan (CPT-11)  Celecoxib Compound M5 Retinoids Colon Celecoxib Compound M5 DFMO Colon Celecoxib Compound M5 Ursodeoxycholi Colon c acid  Celecoxib Compound M5 calcium Colon carbonate  Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 sulindac Colon Sulfone  Celecoxib Compound M5 Carboplatin Brain Celecoxib Compound M5 Goserelin Prostate Acetate  Celecoxib Compound M5 Ketoconazole Prostate Celecoxib Compound M5 Cisplatin Celecoxib Compound M7 Anastrozole Breast Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Fluorouracil	Colon,
Celecoxib Compound M5 Retinoids Colon Celecoxib Compound M5 DFMO Colon Celecoxib Compound M5 Ursodeoxycholi Colon c acid Celecoxib Compound M5 calcium Colon carbonate Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 sulindac Colon sulfone Celecoxib Compound M5 Carboplatin Brain Celecoxib Compound M5 Goserelin Prostate Acetate Celecoxib Compound M5 Ketoconazole Prostate Celecoxib Compound M5 Cisplatin Celecoxib Compound M7 Capecitabine Breast Celecoxib Compound M7 Anastrozole Breast				Bladder
Celecoxib Compound M5 Retinoids Colon  Celecoxib Compound M5 DFMO Colon  Celecoxib Compound M5 Ursodeoxycholi Colon  c acid  Celecoxib Compound M5 calcium Colon  carbonate  Celecoxib Compound M5 selenium Colon  Celecoxib Compound M5 sulindac Colon  sulfone  Celecoxib Compound M5 Carboplatin Brain  Celecoxib Compound M5 Goserelin Prostate  Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Anastrozole Breast  Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Irinotecan	Colon
Celecoxib Compound M5 DFMO Colon  Celecoxib Compound M5 Ursodeoxycholi Colon			(CPT-11)	
Celecoxib Compound M5 Ursodeoxycholi Colon c acid  Celecoxib Compound M5 calcium Colon carbonate  Celecoxib Compound M5 selenium Colon  Celecoxib Compound M5 sulindac Colon sulfone  Celecoxib Compound M5 Carboplatin Brain  Celecoxib Compound M5 Goserelin Prostate  Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Capecitabine Breast  Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Retinoids	Colon
Celecoxib Compound M5 calcium Colon carbonate  Celecoxib Compound M5 selenium Colon Celecoxib Compound M5 sulindac Colon sulfone  Celecoxib Compound M5 Carboplatin Brain Celecoxib Compound M5 Goserelin Prostate Acetate  Celecoxib Compound M5 Ketoconazole Prostate Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Capecitabine Breast Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	DFMO	Colon
Celecoxib Compound M5 calcium carbonate  Celecoxib Compound M5 selenium Colon  Celecoxib Compound M5 sulindac Colon  Sulfone  Celecoxib Compound M5 Carboplatin Brain  Celecoxib Compound M5 Goserelin Prostate  Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Capecitabine Breast  Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Ursodeoxycholi	Colon
Celecoxib Compound M5 selenium Colon  Celecoxib Compound M5 sulindac Colon sulfone  Celecoxib Compound M5 Carboplatin Brain  Celecoxib Compound M5 Goserelin Prostate Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Capecitabine Breast  Celecoxib Compound M7 Capecitabine Breast			c acid	
Celecoxib Compound M5 selenium Colon  Celecoxib Compound M5 sulindac Colon sulfone  Celecoxib Compound M5 Carboplatin Brain  Celecoxib Compound M5 Goserelin Prostate  Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Anastrozole Breast  Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	calcium	Colon
Celecoxib Compound M5 sulindac Colon sulfone  Celecoxib Compound M5 Carboplatin Brain  Celecoxib Compound M5 Goserelin Prostate  Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Anastrozole Breast  Celecoxib Compound M7 Capecitabine Breast			carbonate	
Sulfone  Celecoxib Compound M5 Carboplatin Brain  Celecoxib Compound M5 Goserelin Prostate Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Anastrozole Breast  Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	selenium	Colon
Celecoxib Compound M5 Carboplatin Brain  Celecoxib Compound M5 Goserelin Prostate Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Anastrozole Breast  Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	sulindac	Colon
Celecoxib Compound M5 Goserelin Prostate Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Anastrozole Breast  Celecoxib Compound M7 Capecitabine Breast		·	sulfone	
Acetate  Celecoxib Compound M5 Ketoconazole Prostate  Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Anastrozole Breast  Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Carboplatin	Brain
CelecoxibCompound M5KetoconazoleProstateCelecoxibCompound M5CisplatinCelecoxibCompound M7AnastrozoleBreastCelecoxibCompound M7CapecitabineBreast	Celecoxib	Compound M5	Goserelin	Prostate
Celecoxib Compound M5 Cisplatin  Celecoxib Compound M7 Anastrozole Breast  Celecoxib Compound M7 Capecitabine Breast			Acetate	
Celecoxib Compound M7 Anastrozole Breast Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Ketoconazole	Prostate
Celecoxib Compound M7 Capecitabine Breast	Celecoxib	Compound M5	Cisplatin	
	Celecoxib	Compound M7	Anastrozole	Breast
Celecoxib Compound M7 Docetaxel Breast,	Celecoxib	Compound M7	Capecitabine	Breast
	Celecoxib	Compound M7	Docetaxel	Breast,
Pancreas				Pancreas

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Celecoxib Compound M7 Gemcitable Breast  Celecoxib Compound M7 Megestrol Breast  Celecoxib Compound M7 Paclitaxel Breast  Celecoxib Compound M7 Tamoxifen Breast  Celecoxib Compound M7 Toremifene Breast  Celecoxib Compound M7 Toremifene Breast,  Lung  Celecoxib Compound M7 Topotecan Lung  Celecoxib Compound M7 Topotecan Lung  Celecoxib Compound M7 Fluorouracil Colon,  Bladder  Celecoxib Compound M7 Fluorouracil Colon,  Celecoxib Compound M7 Retinoids Colon  (CPT-11)  Celecoxib Compound M7 Retinoids Colon  Celecoxib Compound M7 Ursodeoxycholi Colon  Celecoxib Compound M7 Calcium Colon  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 Selenium Colon  Celecoxib Compound M7 Selenium Colon  Celecoxib Compound M7 Selenium Colon  Celecoxib Compound M7 Selenium Prostate  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate  Celecoxib Compound M7 Carboplatin Prostate  Celecoxib Compound M7 Carboplatin Prostate  Celecoxib Compound M7 Carboplatin Prostate  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Carboplatin Brain	0-1	Company 3 357	0	Drocat
Celecoxib Compound M7 Megestrol Breast Celecoxib Compound M7 Paclitaxel Breast Celecoxib Compound M7 Tamoxifen Breast Celecoxib Compound M7 Toremifene Breast, Lung Celecoxib Compound M7 Toremifene Breast, Lung Celecoxib Compound M7 Topotecan Lung Celecoxib Compound M7 Etoposide Colon Celecoxib Compound M7 Fluorouracil Colon, Bladder Celecoxib Compound M7 Irinotecan Colon (CPT-11) Celecoxib Compound M7 Retinoids Colon Celecoxib Compound M7 DFMO Colon Celecoxib Compound M7 Ursodeoxycholi Colon c acid Celecoxib Compound M7 calcium Colon Celecoxib Compound M7 selenium Colon Celecoxib Compound M7 selenium Colon Celecoxib Compound M7 Selenium Colon Celecoxib Compound M7 Selenium Colon Celecoxib Compound M7 Selenium Prostate Celecoxib Compound M7 Goserelin Prostate Celecoxib Compound M7 Ketoconazole Prostate Celecoxib Compound M7 Ketoconazole Prostate Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	Gemcitabine	Breast
Celecoxib Compound M7 Paclitaxel Breast  Celecoxib Compound M7 Tamoxifen Breast  Celecoxib Compound M7 Toremifene Breast, Lung  Celecoxib Compound M7 Vinorelbine Lung  Celecoxib Compound M7 Topotecan Lung  Celecoxib Compound M7 Etoposide Colon  Celecoxib Compound M7 Fluorouracil Colon, Bladder  Celecoxib Compound M7 Irinotecan Colon (CPT-11)  Celecoxib Compound M7 Retinoids Colon  Celecoxib Compound M7 DFMO Colon  Celecoxib Compound M7 Ursodeoxycholi Colon  c acid  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 Selenium Colon  Celecoxib Compound M7 Selenium Prostate  Celecoxib Compound M7 Goserelin Prostate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin			Letrozole	Breast
Celecoxib Compound M7 Tamoxifen Breast  Celecoxib Compound M7 Toremifene Breast, Lung  Celecoxib Compound M7 Vinorelbine Lung  Celecoxib Compound M7 Topotecan Lung  Celecoxib Compound M7 Etoposide Colon  Celecoxib Compound M7 Fluorouracil Colon, Bladder  Celecoxib Compound M7 Irinotecan Colon (CPT-11)  Celecoxib Compound M7 Retinoids Colon  Celecoxib Compound M7 DFMO Colon  Celecoxib Compound M7 Ursodeoxycholi Colon  c acid  Celecoxib Compound M7 calcium Colon  carbonate  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 Sulindac Colon  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate  Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	Megestrol	Breast
Celecoxib Compound M7 Toremifene Breast, Lung  Celecoxib Compound M7 Vinorelbine Lung  Celecoxib Compound M7 Topotecan Lung  Celecoxib Compound M7 Etoposide Colon  Celecoxib Compound M7 Fluorouracil Colon, Bladder  Celecoxib Compound M7 Irinotecan Colon (CPT-11)  Celecoxib Compound M7 Retinoids Colon  Celecoxib Compound M7 DFMO Colon  Celecoxib Compound M7 Ursodeoxycholi Colon  c acid  Celecoxib Compound M7 calcium Colon  carbonate  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 Selenium Colon  Celecoxib Compound M7 Sulindac Colon  Sulfone  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate  Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	Paclitaxel	Breast
Celecoxib Compound M7 Vinorelbine Lung Celecoxib Compound M7 Topotecan Lung Celecoxib Compound M7 Etoposide Colon Celecoxib Compound M7 Fluorouracil Colon, Bladder Celecoxib Compound M7 Irinotecan Colon (CPT-11) Celecoxib Compound M7 Retinoids Colon Celecoxib Compound M7 DFMO Colon Celecoxib Compound M7 Ursodeoxycholi Colon c acid Celecoxib Compound M7 calcium Colon Celecoxib Compound M7 selenium Colon Celecoxib Compound M7 selenium Colon Celecoxib Compound M7 Sulindac Colon Sulfone Celecoxib Compound M7 Carboplatin Brain Celecoxib Compound M7 Goserelin Prostate Acetate Celecoxib Compound M7 Ketoconazole Prostate Celecoxib Compound M7 Cisplatin Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	Tamoxifen	Breast
Celecoxib Compound M7 Vinorelbine Lung  Celecoxib Compound M7 Topotecan Lung  Celecoxib Compound M7 Etoposide Colon  Celecoxib Compound M7 Fluorouracil Colon, Bladder  Celecoxib Compound M7 Irinotecan Colon (CPT-11)  Celecoxib Compound M7 Retinoids Colon  Celecoxib Compound M7 DFMO Colon  Celecoxib Compound M7 Ursodeoxycholi Colon c acid  Celecoxib Compound M7 calcium Colon carbonate  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 Sulindac Colon  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate  Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	Toremifene	Breast,
Celecoxib Compound M7 Topotecan Lung  Celecoxib Compound M7 Etoposide Colon  Celecoxib Compound M7 Fluorouracil Colon, Bladder  Celecoxib Compound M7 Irinotecan Colon (CPT-11)  Celecoxib Compound M7 Retinoids Colon  Celecoxib Compound M7 DFMO Colon  Celecoxib Compound M7 Ursodeoxycholi Colon  c acid  Celecoxib Compound M7 calcium Colon  carbonate  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 sulindac Colon  Celecoxib Compound M7 Sulindac Colon  Celecoxib Compound M7 Goserelin Brain  Celecoxib Compound M7 Goserelin Prostate  Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin				Lung
Celecoxib Compound M7 Etoposide Colon  Celecoxib Compound M7 Fluorouracil Colon, Bladder  Celecoxib Compound M7 Irinotecan Colon (CPT-11)  Celecoxib Compound M7 Retinoids Colon  Celecoxib Compound M7 DFMO Colon  Celecoxib Compound M7 Ursodeoxycholi Colon  c acid  Celecoxib Compound M7 calcium Colon  carbonate  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 sulindac Colon  Celecoxib Compound M7 Sulindac Colon  Celecoxib Compound M7 Goserelin Brain  Celecoxib Compound M7 Goserelin Prostate  Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	Vinorelbine	Lung
Celecoxib Compound M7 Fluorouracil Colon, Bladder  Celecoxib Compound M7 Irinotecan Colon (CPT-11)  Celecoxib Compound M7 Retinoids Colon  Celecoxib Compound M7 DFMO Colon  Celecoxib Compound M7 Ursodeoxycholi Colon c acid  Celecoxib Compound M7 calcium Colon carbonate  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 sulindac Colon sulfone  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	Topotecan	Lung
Celecoxib Compound M7 Irinotecan Colon (CPT-11)  Celecoxib Compound M7 Retinoids Colon Celecoxib Compound M7 DFMO Colon Celecoxib Compound M7 Ursodeoxycholi Colon c acid  Celecoxib Compound M7 calcium Colon carbonate  Celecoxib Compound M7 selenium Colon Celecoxib Compound M7 sulindac Colon Sulfone  Celecoxib Compound M7 Carboplatin Brain Celecoxib Compound M7 Goserelin Prostate Acetate  Celecoxib Compound M7 Ketoconazole Prostate Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	Etoposide	Colon
Celecoxib Compound M7 Irinotecan (CPT-11)  Celecoxib Compound M7 Retinoids Colon  Celecoxib Compound M7 DFMO Colon  Celecoxib Compound M7 Ursodeoxycholi Colon  c acid  Celecoxib Compound M7 calcium Colon  carbonate  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 sulindac Colon  Sulfone  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate  Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	Fluorouracil	Colon,
Celecoxib Compound M7 Retinoids Colon  Celecoxib Compound M7 DFMO Colon  Celecoxib Compound M7 Ursodeoxycholi Colon c acid  Celecoxib Compound M7 calcium Colon carbonate  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 sulindac Colon sulfone  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate  Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin				Bladder
Celecoxib Compound M7 Retinoids Colon  Celecoxib Compound M7 DFMO Colon  Celecoxib Compound M7 Ursodeoxycholi Colon c acid  Celecoxib Compound M7 calcium Colon carbonate  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 sulindac Colon sulfone  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	Irinotecan	Colon
Celecoxib Compound M7 DFMO Colon  Celecoxib Compound M7 Ursodeoxycholi Colon			(CPT-11)	
Celecoxib Compound M7 Ursodeoxycholi Colon c acid  Celecoxib Compound M7 calcium Colon carbonate  Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 sulindac Colon sulfone  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	Retinoids	Colon
Celecoxib Compound M7 calcium Colon carbonate  Celecoxib Compound M7 selenium Colon Celecoxib Compound M7 sulindac Colon sulfone  Celecoxib Compound M7 Carboplatin Brain Celecoxib Compound M7 Goserelin Prostate Acetate  Celecoxib Compound M7 Ketoconazole Prostate Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	DFMO	Colon
Celecoxib Compound M7 calcium Colon carbonate  Celecoxib Compound M7 selenium Colon Celecoxib Compound M7 sulindac Colon sulfone  Celecoxib Compound M7 Carboplatin Brain Celecoxib Compound M7 Goserelin Prostate Acetate  Celecoxib Compound M7 Ketoconazole Prostate Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	Ursodeoxycholi	Colon
Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 sulindac Colon sulfone  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin			c acid	
Celecoxib Compound M7 selenium Colon  Celecoxib Compound M7 sulindac Colon sulfone  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Compound M7 Cisplatin	Celecoxib	Compound M7	calcium	Colon
Celecoxib Compound M7 sulindac Colon sulfone  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Bay-12-9566 Anastrozole Colon			carbonate	
Sulfone  Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Bay-12-9566 Anastrozole Colon	Celecoxib	Compound M7	selenium	Colon
Celecoxib Compound M7 Carboplatin Brain  Celecoxib Compound M7 Goserelin Prostate Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Bay-12-9566 Anastrozole Colon	Celecoxib	Compound M7	sulindac	Colon
Celecoxib Compound M7 Goserelin Prostate Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Bay-12-9566 Anastrozole Colon			sulfone	
Acetate  Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Bay-12-9566 Anastrozole Colon	Celecoxib	Compound M7	Carboplatin	Brain
Celecoxib Compound M7 Ketoconazole Prostate  Celecoxib Compound M7 Cisplatin  Celecoxib Bay-12-9566 Anastrozole Colon	Celecoxib	Compound M7	Goserelin	Prostate
Celecoxib Compound M7 Cisplatin  Celecoxib Bay-12-9566 Anastrozole Colon			Acetate	
Celecoxib Bay-12-9566 Anastrozole Colon	Celecoxib	Compound M7	Ketoconazole	Prostate
	Celecoxib	Compound M7	Cisplatin	
		· · · · · · · · · · · · · · · · · · ·		
Celecoxib Bay-12-9566 Capecitabine Brain	Celecoxib	Bay-12-9566	Anastrozole	Colon
	Celecoxib	Bay-12-9566	Capecitabine	Brain

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Celecoxib	Bay-12-9566	Docetaxel	Prostate
Celecoxib	Bay-12-9566	Gemcitabine	Prostate
Celecoxib	Bay-12-9566	Letrozole	Breast
Celecoxib	Bay-12-9566	Megestrol	Breast
Celecoxib	Bay-12-9566	Paclitaxel	Breast
Celecoxib	Bay-12-9566	Tamoxifen	Breast
Celecoxib	Bay-12-9566	Toremifene	Breast
Celecoxib	Bay-12-9566	Vinorelbine	Breast,
		:	Lung
Celecoxib	Bay-12-9566	Topotecan	Lung
Celecoxib	Bay-12-9566	Etoposide	Lung
Celecoxib	Bay-12-9566	Fluorouracil	Colon
Celecoxib	Bay-12-9566	Irinotecan	Colon,
		(CPT-11)	Bladder
Celecoxib	Bay-12-9566	Retinoids	Colon
Celecoxib	Bay-12-9566	DFMO	Colon
Celecoxib	Bay-12-9566	Ursodeoxycholi	Colon
		c acid	
Celecoxib	Bay-12-9566	calcium	Colon
		carbonate	
Celecoxib	Bay-12-9566	selenium	Colon
Celecoxib	Bay-12-9566	sulindac	Colon
		sulfone	
Celecoxib	Bay-12-9566	Carboplatin	Brain
Celecoxib	Bay-12-9566	Goserelin	Prostate
		Acetate	
Celecoxib	Bay-12-9566	Ketoconazole	Prostate
Celecoxib	Bay-12-9566	Cisplatin	
Celecoxib	Metastat	Anastrozole	Breast
Celecoxib	Metastat	Capecitabine	Breast
Celecoxib	Metastat	Docetaxel	Breast
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Celecoxib Metastat Letrozole Breast Celecoxib Metastat Megestrol Breast Celecoxib Metastat Paclitaxel Breast Celecoxib Metastat Tamoxifen Breast Celecoxib Metastat Toremifene Breast Celecoxib Metastat Toremifene Breast Celecoxib Metastat Topotecan Lung Celecoxib Metastat Etoposide Lung Celecoxib Metastat Fluorouracil Colon Celecoxib Metastat Fluorouracil Colon (CPT-11) Bladder Celecoxib Metastat Retinoids Colon Celecoxib Metastat DFMO Colon Celecoxib Metastat Ursodeoxycholi Colon Celecoxib Metastat Calcium Colon Celecoxib Metastat Selenium Colon Celecoxib Metastat Selenium Colon Celecoxib Metastat Selenium Colon Celecoxib Metastat Carboplatin Brain Celecoxib Metastat Carboplatin Brain Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib D-2163 Anastrozole Breast Celecoxib D-2163 Capecitabine Breast Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	Gemcitabine	Breast,
Celecoxib Metastat Paclitaxel Breast Celecoxib Metastat Paclitaxel Breast Celecoxib Metastat Tamoxifen Breast Celecoxib Metastat Toremifene Breast Celecoxib Metastat Toremifene Breast Celecoxib Metastat Topotecan Lung Celecoxib Metastat Etoposide Lung Celecoxib Metastat Fluorouracil Colon Celecoxib Metastat Fluorouracil Colon (CPT-11) Bladder Celecoxib Metastat Retinoids Colon Celecoxib Metastat Ursodeoxycholi Colon Celecoxib Metastat Calcium Colon Cacid Celecoxib Metastat Selenium Colon Carbonate Celecoxib Metastat Selenium Colon Carbonate Celecoxib Metastat Selenium Colon Celecoxib Metastat Selenium Prostate Celecoxib Metastat Carboplatin Brain Celecoxib Metastat Carbonazole Prostate Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib D-2163 Capecitabine Breast				Pancreas
Celecoxib Metastat Paclitaxel Breast Celecoxib Metastat Tamoxifen Breast Celecoxib Metastat Toremifene Breast Celecoxib Metastat Vinorelbine Breast, Lung Celecoxib Metastat Topotecan Lung Celecoxib Metastat Etoposide Lung Celecoxib Metastat Fluorouracil Colon Celecoxib Metastat Fluorouracil Colon Celecoxib Metastat Fluorouracil Colon Celecoxib Metastat Retinoids Colon Celecoxib Metastat DFMO Colon Celecoxib Metastat Ursodeoxycholi Colon Celecoxib Metastat Calcium Colon Carbonate Celecoxib Metastat Selenium Colon Celecoxib Metastat Sulindac Colon Celecoxib Metastat Carboplatin Brain Celecoxib Metastat Carboplatin Brain Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	Letrozole	Breast
Celecoxib Metastat Tamoxifen Breast Celecoxib Metastat Toremifene Breast Celecoxib Metastat Vinorelbine Breast, Lung Celecoxib Metastat Topotecan Lung Celecoxib Metastat Etoposide Lung Celecoxib Metastat Fluorouracil Colon Celecoxib Metastat Irinotecan Colon, (CPT-11) Bladder Celecoxib Metastat DFMO Colon Celecoxib Metastat Ursodeoxycholi Colon Celecoxib Metastat Calcium Colon Celecoxib Metastat selenium Colon Celecoxib Metastat Selenium Colon Celecoxib Metastat Sulindac Colon Celecoxib Metastat Carboplatin Brain Celecoxib Metastat Carboplatin Brain Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib D-2163 Capecitabine Breast Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	Megestrol	Breast
Celecoxib Metastat Toremifene Breast Celecoxib Metastat Vinorelbine Breast, Lung Celecoxib Metastat Topotecan Lung Celecoxib Metastat Etoposide Lung Celecoxib Metastat Fluorouracil Colon Celecoxib Metastat Irinotecan Colon, (CPT-11) Bladder Celecoxib Metastat Retinoids Colon Celecoxib Metastat DFMO Colon Celecoxib Metastat Ursodeoxycholi Colon c acid Celecoxib Metastat calcium Colon Carbonate Celecoxib Metastat selenium Colon Celecoxib Metastat Selenium Colon Celecoxib Metastat Carboplatin Brain Celecoxib Metastat Carboplatin Brain Celecoxib Metastat Ketoconazole Prostate Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib Metastat Cisplatin Celecoxib D-2163 Anastrozole Breast Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	Paclitaxel	Breast
Celecoxib Metastat Vinorelbine Breast, Lung  Celecoxib Metastat Topotecan Lung  Celecoxib Metastat Etoposide Lung  Celecoxib Metastat Fluorouracil Colon  Celecoxib Metastat Irinotecan Colon, (CPT-11) Bladder  Celecoxib Metastat DFMO Colon  Celecoxib Metastat Ursodeoxycholi Colon  Cacid  Celecoxib Metastat calcium Colon  carbonate  Celecoxib Metastat selenium Colon  Celecoxib Metastat Selenium Colon  Carbonate  Celecoxib Metastat Carboplatin Brain  Celecoxib Metastat Goserelin Prostate  Acetate  Celecoxib Metastat Cisplatin  Celecoxib Metastat Cisplatin  Celecoxib Metastat Cisplatin  Celecoxib Metastat Cisplatin  Celecoxib D-2163 Anastrozole Breast  Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	Tamoxifen	Breast
Celecoxib Metastat Topotecan Lung  Celecoxib Metastat Etoposide Lung  Celecoxib Metastat Fluorouracil Colon  Celecoxib Metastat Irinotecan Colon,	Celecoxib	Metastat	Toremifene	Breast
Celecoxib Metastat Etoposide Lung Celecoxib Metastat Etoposide Lung Celecoxib Metastat Fluorouracil Colon Celecoxib Metastat Fluorouracil Colon,	Celecoxib	Metastat	Vinorelbine	Breast,
Celecoxib Metastat Etoposide Lung  Celecoxib Metastat Fluorouracil Colon  Celecoxib Metastat Irinotecan Colon,				Lung
Celecoxib Metastat Fluorouracil Colon  Celecoxib Metastat Irinotecan Colon,	Celecoxib	Metastat	Topotecan	Lung
Celecoxib Metastat Irinotecan Colon, (CPT-11) Bladder  Celecoxib Metastat Retinoids Colon  Celecoxib Metastat DFMO Colon  Celecoxib Metastat Ursodeoxycholi Colon c acid  Celecoxib Metastat calcium Colon carbonate  Celecoxib Metastat selenium Colon  Celecoxib Metastat sulindac Colon  Sulfone  Celecoxib Metastat Carboplatin Brain  Celecoxib Metastat Goserelin Prostate  Acetate  Celecoxib Metastat Ketoconazole Prostate  Celecoxib Metastat Cisplatin  Celecoxib Metastat Cisplatin  Celecoxib Metastat Cisplatin  Celecoxib D-2163 Anastrozole Breast  Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	Etoposide	Lung
Celecoxib Metastat Retinoids Colon  Celecoxib Metastat DFMO Colon  Celecoxib Metastat Ursodeoxycholi Colon c acid  Celecoxib Metastat calcium Colon carbonate  Celecoxib Metastat selenium Colon  Celecoxib Metastat sulindac Colon sulfone  Celecoxib Metastat Carboplatin Brain  Celecoxib Metastat Goserelin Prostate  Acetate  Celecoxib Metastat Ketoconazole Prostate  Celecoxib Metastat Cisplatin  Celecoxib D-2163 Anastrozole Breast  Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	Fluorouracil	Colon
CelecoxibMetastatRetinoidsColonCelecoxibMetastatDFMOColonCelecoxibMetastatUrsodeoxycholi c acidColonCelecoxibMetastatcalcium carbonateColonCelecoxibMetastatseleniumColonCelecoxibMetastatsulindac sulfoneColonCelecoxibMetastatCarboplatinBrainCelecoxibMetastatGoserelin AcetateProstateCelecoxibMetastatKetoconazoleProstateCelecoxibMetastatCisplatinCelecoxibD-2163AnastrozoleBreastCelecoxibD-2163CapecitabineBreast	Celecoxib	Metastat	Irinotecan	Colon,
CelecoxibMetastatDFMOColonCelecoxibMetastatUrsodeoxycholi c acidColonCelecoxibMetastatcalcium carbonateColonCelecoxibMetastatseleniumColonCelecoxibMetastatsulindac sulfoneColonCelecoxibMetastatCarboplatinBrainCelecoxibMetastatGoserelin AcetateProstateCelecoxibMetastatKetoconazoleProstateCelecoxibMetastatCisplatinCelecoxibD-2163AnastrozoleBreastCelecoxibD-2163CapecitabineBreast			(CPT-11)	Bladder
Celecoxib Metastat Ursodeoxycholi Colon c acid  Celecoxib Metastat calcium Colon carbonate  Celecoxib Metastat selenium Colon Celecoxib Metastat sulindac Colon sulfone  Celecoxib Metastat Carboplatin Brain  Celecoxib Metastat Goserelin Prostate Acetate  Celecoxib Metastat Cisplatin  Celecoxib Metastat Cisplatin  Celecoxib Metastat Cisplatin  Celecoxib D-2163 Anastrozole Breast  Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	Retinoids	Colon
Celecoxib Metastat calcium Colon carbonate  Celecoxib Metastat selenium Colon Celecoxib Metastat sulindac Colon sulfone  Celecoxib Metastat Carboplatin Brain Celecoxib Metastat Goserelin Prostate Acetate  Celecoxib Metastat Ketoconazole Prostate Celecoxib Metastat Cisplatin Celecoxib D-2163 Anastrozole Breast Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	DFMO	Colon
Celecoxib Metastat calcium carbonate  Celecoxib Metastat selenium Colon  Celecoxib Metastat sulindac Colon  Sulfone  Celecoxib Metastat Carboplatin Brain  Celecoxib Metastat Goserelin Prostate  Acetate  Celecoxib Metastat Ketoconazole Prostate  Celecoxib Metastat Cisplatin  Celecoxib D-2163 Anastrozole Breast  Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	Ursodeoxycholi	Colon
Celecoxib Metastat selenium Colon  Celecoxib Metastat sulindac Colon sulfone  Celecoxib Metastat Carboplatin Brain  Celecoxib Metastat Goserelin Prostate Acetate  Celecoxib Metastat Ketoconazole Prostate  Celecoxib Metastat Cisplatin  Celecoxib D-2163 Anastrozole Breast  Celecoxib D-2163 Capecitabine Breast			c acid	
CelecoxibMetastatseleniumColonCelecoxibMetastatsulindac sulfoneColonCelecoxibMetastatCarboplatinBrainCelecoxibMetastatGoserelin AcetateProstateCelecoxibMetastatKetoconazoleProstateCelecoxibMetastatCisplatinCelecoxibD-2163AnastrozoleBreastCelecoxibD-2163CapecitabineBreast	Celecoxib	Metastat	calcium	Colon
Celecoxib Metastat sulindac Colon sulfone  Celecoxib Metastat Carboplatin Brain  Celecoxib Metastat Goserelin Prostate Acetate  Celecoxib Metastat Ketoconazole Prostate  Celecoxib Metastat Cisplatin  Celecoxib D-2163 Anastrozole Breast  Celecoxib D-2163 Capecitabine Breast			carbonate	
Sulfone  Celecoxib Metastat Carboplatin Brain  Celecoxib Metastat Goserelin Prostate Acetate  Celecoxib Metastat Ketoconazole Prostate  Celecoxib Metastat Cisplatin  Celecoxib D-2163 Anastrozole Breast  Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	selenium	Colon
CelecoxibMetastatCarboplatinBrainCelecoxibMetastatGoserelinProstateAcetateAcetateCelecoxibMetastatKetoconazoleProstateCelecoxibMetastatCisplatinCelecoxibD-2163AnastrozoleBreastCelecoxibD-2163CapecitabineBreast	Celecoxib	Metastat	sulindac	Colon
Celecoxib Metastat Goserelin Prostate Acetate  Celecoxib Metastat Ketoconazole Prostate  Celecoxib Metastat Cisplatin  Celecoxib D-2163 Anastrozole Breast  Celecoxib D-2163 Capecitabine Breast			sulfone	
Acetate  Celecoxib Metastat Ketoconazole Prostate  Celecoxib Metastat Cisplatin  Celecoxib D-2163 Anastrozole Breast  Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	Carboplatin	Brain
CelecoxibMetastatKetoconazoleProstateCelecoxibMetastatCisplatinCelecoxibD-2163AnastrozoleBreastCelecoxibD-2163CapecitabineBreast	Celecoxib	Metastat	Goserelin	Prostate
CelecoxibMetastatCisplatinCelecoxibD-2163AnastrozoleBreastCelecoxibD-2163CapecitabineBreast			Acetate	
Celecoxib D-2163 Anastrozole Breast Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	Ketoconazole	Prostate
Celecoxib D-2163 Capecitabine Breast	Celecoxib	Metastat	Cisplatin	
	Celecoxib	D-2163	Anastrozole	Breast
Celecoxib D-2163 Docetaxel Breast	Celecoxib	D-2163	Capecitabine	Breast
	Celecoxib	D-2163	Docetaxel	Breast

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Celecoxib	D-2163	Gemcitabine	Breast,
			Pancreas
Celecoxib	D-2163	Letrozole	Breast
Celecoxib	D-2163	Megestrol	Breast
Celecoxib	D-2163	Paclitaxel	Breast
Celecoxib	D-2163	Tamoxifen	Breast
Celecoxib	D-2163	Toremifene	Breast
Celecoxib	D-2163	Vinorelbine	Breast,
			Lung
Celecoxib	D-2163	Topotecan	Lung
Celecoxib	D-2163	Etoposide	Lung
Celecoxib	D-2163	Fluorouracil	Colon
Celecoxib	D-2163	Irinotecan	Colon,
		(CPT-11)	Bladder
Celecoxib	D-2163	Retinoids	Colon
Celecoxib	D-2163	DFMO	Colon
Celecoxib	D-2163	Ursodeoxycholi	Colon
		c acid	
Celecoxib	D-2163	calcium	Colon
		carbonate	
Celecoxib	D-2163	selenium	Colon
Celecoxib	D-2163	sulindac	Colon
		sulfone	
Celecoxib	D-2163	Carboplatin	Brain
Celecoxib	D-2163	Goserelin	Prostate
		Acetate	
Celecoxib	D-2163	Ketoconazole	Prostate
Celecoxib	D-2163	Cisplatin	
Celecoxib	D-1927	Anastrozole	Breast
Celecoxib	D-1927	Capecitabine	Breast
Celecoxib	D-1927	Docetaxel	Breast

Celecoxib	D-1927	Gemcitabine	Breast,
			Pancreas
Celecoxib	D-1927	Letrozole	Breast
Celecoxib	D-1927	Megestrol	Breast
Celecoxib	D-1927	Paclitaxel	Breast
Celecoxib	D-1927	Tamoxifen	Breast
Celecoxib	D-1927	Toremifene	Breast
Celecoxib	D-1927	Vinorelbine	Breast,
			Lung
Celecoxib	D-1927	Topotecan	Lung
Celecoxib	D-1927	Etoposide	Lung
Celecoxib	D-1927	Fluorouracil	Colon
Celecoxib	D-1927	Irinotecan	Colon,
		(CPT-11)	Bladder
Celecoxib	D-1927	Retinoids	Colon
Celecoxib	D-1927	DFMO	Colon
Celecoxib	D-1927	Ursodeoxycholi	Colon
		c acid	
Celecoxib	D-1927	calcium	Colon
		carbonate	
Celecoxib	D-1927	selenium	Colon
Celecoxib	D-1927	sulindac	Colon
		sulfone	
Celecoxib	D-1927	Carboplatin	Brain
Celecoxib	D-1927	Goserelin	Prostate
		Acetate	
Celecoxib	D-1927	Ketoconazole	Prostate
Celecoxib	D-1927	Cisplatin	
Celecoxib	Compound M1	Anastrozole	Breast
Celecoxib	Compound M1	Capecitabine	Breast
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Celecoxib	Compound M1	Docetaxel	Breast
Celecoxib	Compound M1	Gemcitabine	
Celecoxid	Compound MI	Gemcitabine	Breast,
			Pancreas
Celecoxib	Compound M1	Letrozole	Breast
Celecoxib	Compound M1	Megestrol	Breast
Celecoxib	Compound M1	Paclitaxel	Breast
Celecoxib	Compound M1	Tamoxifen	Breast
Celecoxib	Compound M1	Toremifene	Breast
Celecoxib	Compound M1	Vinorelbine	Breast,
			Lung
Celecoxib	Compound M1	Topotecan	Lung
Celecoxib	Compound M1	Etoposide	Lung
Celecoxib	Compound M1	Fluorouracil	Colon
Celecoxib	Compound M1	Irinotecan	Colon,
		(CPT-11)	Bladder
Celecoxib	Compound M1	Retinoids	Colon
Celecoxib	Compound M1	DFMO	Colon
Celecoxib	Compound M1	Ursodeoxycholi	Colon
		c acid	
Celecoxib	Compound M1	calcium	Colon
		carbonate	
Celecoxib	Compound M1	selenium	Colon
Celecoxib	Compound M1	sulindac	Colon
		sulfone	
Celecoxib	Compound M1	Carboplatin	Brain
Celecoxib	Compound M1	Goserelin	Prostate
		Acetate	
Celecoxib	Compound M1	Ketoconazole	Prostate
Celecoxib	Compound M1	Cisplatin	······································
Celecoxib	Compound M2	Anastrozole	Breast
Celecoxib	Compound M2	Capecitabine	Breast
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Celecoxib	Compound M2	Docetaxel	Breast
Celecoxib	Compound M2	Gemcitabine	Breast,
			Pancreas
Celecoxib	Compound M2	Letrozole	Breast
Celecoxib	Compound M2	Megestrol	Breast
Celecoxib	Compound M2	Paclitaxel	Breast
Celecoxib	Compound M2	Tamoxifen	Breast
Celecoxib	Compound M2	Toremifene	Breast
Celecoxib	Compound M2	Vinorelbine	Breast,
			Lung
Celecoxib	Compound M2	Topotecan	Lung
Celecoxib	Compound M2	Etoposide	Lung
Celecoxib	Compound M2	Fluorouracil	Colon
Celecoxib	Compound M2	Irinotecan	Colon,
		(CPT-11)	Bladder
Celecoxib	Compound M2	Retinoids	Colon
Celecoxib	Compound M2	DFMO	Colon
Celecoxib	Compound M2	Ursodeoxycholi	Colon
		c acid	
Celecoxib	Compound M2	calcium	Colon
		carbonate	
Celecoxib	Compound M2	selenium	Colon
Celecoxib	Compound M2	sulindac	Colon
		sulfone	•
Celecoxib	Compound M2	Carboplatin	Brain
Celecoxib	Compound M2	Goserelin	Prostate
		Acetate	
Celecoxib	Compound M2	Ketoconazole	Prostate
Celecoxib	Compound M2	Cisplatin	
Celecoxib	Compound M3	Anastrozole	Breast
Celecoxib	Compound M3	Capecitabine	Breast

Celecoxib	Compound M3	Docetaxel	Breast
Celecoxib	Compound M3	Gemcitabine	Breast,
			Pancreas
Celecoxib	Compound M3	Letrozole	Breast
Celecoxib	Compound M3	Megestrol	Breast
Celecoxib	Compound M3	Paclitaxel	Breast
Celecoxib	Compound M3	Tamoxifen	Breast
Celecoxib	Compound M3	Toremifene	Breast
Celecoxib	Compound M3	Vinorelbine	Breast,
			Lung
Celecoxib	Compound M3	Topotecan	Lung .
Celecoxib	Compound M3	Etoposide	Lung
Celecoxib	Compound M3	Fluorouracil	Colon
Celecoxib	Compound M3	Irinotecan	Colon,
		(CPT-11)	Bladder
Celecoxib	Compound M3	Retinoids	Colon
Celecoxib	Compound M3	DFMO	Colon
Celecoxib	Compound M3	Ursodeoxycholi	Colon
		c acid	
Celecoxib	Compound M3	calcium	Colon
		carbonate	
Celecoxib	Compound M3	selenium	Colon
Celecoxib	Compound M3	sulindac	Colon
		sulfone	
Celecoxib	Compound M3	Carboplatin	Brain
Celecoxib	Compound M3	Goserelin	Prostate
		Acetate	
Celecoxib	Compound M3	Ketoconazole	Prostate
Celecoxib	Compound M3	Cisplatin	
Celecoxib	Compound M4	Anastrozole	Breast
Celecoxib	Compound M4	Capecitabine	Breast
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Celecoxib	Compound M4	Docetaxel	Breast,
			Pancreas
Celecoxib	Compound M4	Gemcitabine	Breast
Celecoxib	Compound M4	Letrozole	Breast
Celecoxib	Compound M4	Megestrol	Breast
Celecoxib	Compound M4	Paclitaxel	Breast
Celecoxib	Compound M4	Tamoxifen	Breast
Celecoxib	Compound M4	Toremifene	Breast,
			Lung
Celecoxib	Compound M4	Vinorelbine	Lung
Celecoxib	Compound M4	Topotecan	Lung
Celecoxib	Compound M4	Etoposide	Colon
Celecoxib	Compound M4	Fluorouracil	Colon,
<u> </u>			Bladder
Celecoxib	Compound M4	Irinotecan	Colon
		(CPT-11)	
Celecoxib	Compound M4	Retinoids	Colon
Celecoxib	Compound M4	DFMO	Colon
Celecoxib	Compound M4	Ursodeoxycholi	Colon
		c acid	
Celecoxib	Compound M4	calcium	Colon
		carbonate	
Celecoxib	Compound M4	selenium	Colon
Celecoxib	Compound M4	sulindac	Colon
		sulfone	<u> </u>
Celecoxib	Compound M4	Carboplatin	Brain
Celecoxib	Compound M4	Goserelin	Prostate
		Acetate	
Celecoxib	Compound M4	Ketoconazole	Prostate
Celecoxib	Compound M4	Cisplatin	
Celecoxib	Compound M5	Anastrozole	Breast

Celecoxib	Compound M5	Capecitabine	Breast
Celecoxib	Compound M5	Docetaxel	Breast,
			Pancreas
Celecoxib	Compound M5	Gemcitabine	Breast
Celecoxib	Compound M5	Letrozole	Breast
Celecoxib	Compound M5	Megestrol	Breast
Celecoxib	Compound M5	Paclitaxel	Breast
Celecoxib	Compound M5	Tamoxifen	Breast
Celecoxib	Compound M5	Toremifene	Breast,
			Lung
Celecoxib	Compound M5	Vinorelbine	Lung
Celecoxib	Compound M5	Topotecan	Lung
Celecoxib	Compound M5	Etoposide	Colon
Celecoxib	Compound M5	Fluorouracil	Colon,
			Bladder
Celecoxib	Compound M5	Irinotecan	Colon
		(CPT-11)	
Celecoxib	Compound M5	Retinoids	Colon
Celecoxib	Compound M5	DFMO	Colon
Celecoxib	Compound M5	Ursodeoxycholi	Colon
		c acid	
Celecoxib	Compound M5	calcium	Colon
		carbonate	
Celecoxib	Compound M5	selenium	Colon
Celecoxib	Compound M5	sulindac	Colon
		sulfone	
Celecoxib	Compound M5	Carboplatin	Brain
Celecoxib	Compound M5	Goserelin	Prostate
		Acetate	
Celecoxib	Compound M5	Ketoconazole	Prostate
Celecoxib	Compound M5	Cisplatin	<del> </del>

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Celecoxib	Compound	м7	Anastrozole	Breast
Celecoxib	Compound	M7	Capecitabine	Breast
Celecoxib	Compound	M7	Docetaxel	Breast,
				Pancreas
Celecoxib	Compound	м7	Gemcitabine	Breast
Celecoxib	Compound	м7	Letrozole	Breast
Celecoxib	Compound	м7	Megestrol	Breast
Celecoxib	Compound	М7	Paclitaxel	Breast
Celecoxib	Compound	м7	Tamoxifen	Breast
Celecoxib	Compound	м7	Toremifene	Breast,
				Lung
Celecoxib	Compound	М7	Vinorelbine	Lung
Celecoxib	Compound	М7	Topotecan	Lung
Celecoxib	Compound	М7	Etoposide	Colon
Celecoxib	Compound	M7	Fluorouracil	Colon,
				Bladder
Celecoxib	Compound	м7	Irinotecan	Colon
			(CPT-11)	
Celecoxib	Compound	M7	Retinoids	Colon
Celecoxib	Compound	м7	DFMO	Colon
Celecoxib	Compound	M7	Ursodeoxycholi	Colon
			c acid	
Celecoxib	Compound	м7	calcium	Colon
			carbonate	
Celecoxib	Compound	М7	selenium	Colon
Celecoxib	Compound	М7	sulindac	Colon
			sulfone	
Celecoxib	Compound	м7	Carboplatin	Brain
Celecoxib	Compound	M7	Goserelin	Prostate
			Acetate	
Celecoxib	Compound	1477	Ketoconazole	Prostate

Celecoxib	Compound M7	Cisplatin	
Rofecoxib	Bay-12-9566	Anastrozole	Colon
Rofecoxib	Bay-12-9566	Capecitabine	Brain
Rofecoxib	Bay-12-9566	Docetaxel	Prostate
Rofecoxib	Bay-12-9566	Gemcitabine	Prostate
Rofecoxib	Bay-12-9566	Letrozole	Breast
Rofecoxib	Bay-12-9566	Megestrol	Breast
Rofecoxib	Bay-12-9566	Paclitaxel	Breast
Rofecoxib	Bay-12-9566	Tamoxifen	Breast
Rofecoxib	Bay-12-9566	Toremifene	Breast
Rofecoxib	Bay-12-9566	Vinorelbine	Breast,
			Lung
Rofecoxib	Bay-12-9566	Topotecan	Lung
Rofecoxib	Bay-12-9566	Etoposide	Lung
Rofecoxib	Bay-12-9566	Fluorouracil	Colon
Rofecoxib	Bay-12-9566	Irinotecan	Colon,
		(CPT-11)	Bladder
Rofecoxib	Bay-12-9566	Retinoids	Colon
Rofecoxib	Bay-12-9566	DFMO	Colon
Rofecoxib	Bay-12-9566	Ursodeoxycholi	Colon
		c acid	
Rofecoxib	Bay-12-9566	calcium	Colon
		carbonate	
Rofecoxib	Bay-12-9566	selenium	Colon
Rofecoxib	Bay-12-9566	sulindac	Colon
		sulfone	
Rofecoxib	Bay-12-9566	Carboplatin	Brain
Rofecoxib	Bay-12-9566	Goserelin	Prostate
		Acetate	
Rofecoxib	Bay-12-9566	Ketoconazole	Prostate

Rofecoxib	Bay-12-9566	Cisplatin	
Rofecoxib	Metastat	Anastrozole	Breast
Rofecoxib	Metastat	Capecitabine	Breast
Rofecoxib	Metastat	Docetaxel	Breast
Rofecoxib	Metastat	Gemcitabine	Breast,
			Pancreas
Rofecoxib	Metastat	Letrozole	Breast
Rofecoxib	Metastat	Megestrol	Breast
Rofecoxib	Metastat	Paclitaxel	Breast
Rofecoxib	Metastat	Tamoxifen	Breast
Rofecoxib	Metastat	Toremifene	Breast
Rofecoxib	Metastat	Vinorelbine	Breast,
			Lung
Rofecoxib	Metastat	Topotecan	Lung
Rofecoxib	Metastat	Etoposide	Lung
Rofecoxib	Metastat	Fluorouracil	Colon
Rofecoxib	Metastat	Irinotecan	Colon,
		(CPT-11)	Bladder
Rofecoxib	Metastat	Retinoids	Colon
Rofecoxib	Metastat	DFMO	Colon
Rofecoxib	Metastat	Ursodeoxycholi	Colon
	·	c acid	
Rofecoxib	Metastat	calcium	Colon
		carbonate	
Rofecoxib	Metastat	selenium	Colon
Rofecoxib	Metastat	sulindac	Colon
		sulfone	
Rofecoxib	Metastat	Carboplatin	Brain
Rofecoxib	Metastat	Goserelin	Prostate
		Acetate	
Rofecoxib	Metastat	Ketoconazole	Prostate

Rofecoxib	Metastat	Cisplatin	
Rofecoxib	D-2163	Anastrozole	Breast
Rofecoxib	D-2163	Capecitabine	Breast
Rofecoxib	D-2163	Docetaxel	Breast
Rofecoxib	D-2163	Gemcitabine	Breast,
			Pancreas
Rofecoxib	D-2163	Letrozole	Breast
Rofecoxib	D-2163	Megestrol	Breast
Rofecoxib	D-2163	Paclitaxel	Breast
Rofecoxib	D-2163	Tamoxifen	Breast
Rofecoxib	D-2163	Toremifene	Breast
Rofecoxib	D-2163	Vinorelbine	Breast,
			Lung
Rofecoxib	D-2163	Topotecan	Lung
Rofecoxib	D-2163	Etoposide	Lung
Rofecoxib	D-2163	Fluorouracil	Colon
Rofecoxib	D-2163	Irinotecan	Colon,
		(CPT-11)	Bladder
Rofecoxib	D-2163	Retinoids	Colon
Rofecoxib	D-2163	DFMO	Colon
Rofecoxib	D-2163	Ursodeoxycholi	Colon
	•	c acid	
Rofecoxib	D-2163	calcium	Colon
		carbonate	
Rofecoxib	D-2163	selenium	Colon
Rofecoxib	D-2163	sulindac	Colon
		sulfone	
Rofecoxib	D-2163	Carboplatin	Brain
Rofecoxib	D-2163	Goserelin	Prostate
		Acetate	
Rofecoxib	D-2163	Ketoconazole	Prostate

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Rofecoxib	D-2163	Cisplatin	
Rofecoxib	D-1927	Anastrozole	Breast
Rofecoxib	D-1927	Capecitabine	Breast
Rofecoxib	D-1927	Docetaxel	Breast
Rofecoxib	D-1927	Gemcitabine	Breast,
·			Pancreas
Rofecoxib	D-1927	Letrozole	Breast
Rofecoxib	D-1927	Megestrol	Breast
Rofecoxib	D-1927	Paclitaxel	Breast
Rofecoxib	D-1927	Tamoxifen	Breast
Rofecoxib	D-1927	Toremifene	Breast
Rofecoxib	D-1927	Vinorelbine	Breast,
			Lung
Rofecoxib	D-1927	Topotecan	Lung
Rofecoxib	D-1927	Etoposide	Lung
Rofecoxib	D-1927	Fluorouracil	Colon
Rofecoxib	D-1927	Irinotecan	Colon,
		(CPT-11)	Bladder
Rofecoxib	D-1927	Retinoids	Colon
Rofecoxib	D-1927	DFMO	Colon
Rofecoxib	D-1927	Ursodeoxycholi	Colon
	·	c acid	
Rofecoxib	D-1927	calcium	Colon
		carbonate	
Rofecoxib	D-1927	selenium	Colon
Rofecoxib	D-1927	sulindac	Colon
		sulfone	
Rofecoxib	D-1927	Carboplatin	Brain
Rofecoxib	D-1927	Goserelin	Prostate
		Acetate	
Rofecoxib	D-1927	Ketoconazole	Prostate

Rofecoxib	D-1927	Cisplatin	
JTE-522	Compound M1	Anastrozole	Breast
JTE-522	Compound M1	Capecitabine	Breast
JTE-522	Compound M1	Docetaxel	Breast
JTE-522	Compound M1	Gemcitabine	Breast,
			Pancreas
JTE-522	Compound M1	Letrozole	Breast
JTE-522	Compound M1	Megestrol	Breast
JTE-522	Compound M1	Paclitaxel	Breast
JTE-522	Compound M1	Tamoxifen	Breast
JTE-522	Compound M1	Toremifene	Breast
JTE-522	Compound M1	Vinorelbine	Breast,
			Lung
JTE-522	Compound M1	Topotecan	Lung
JTE-522	Compound M1	Etoposide	Lung
JTE-522	Compound M1	Fluorouracil	Colon
JTE-522	Compound M1	Irinotecan	Colon,
		(CPT-11)	Bladder
JTE-522	Compound M1	Retinoids	Colon
JTE-522	Compound M1	DFMO	Colon
JTE-522	Compound M1	Ursodeoxycholi	Colon
		c acid	
JTE-522	Compound M1	calcium	Colon
		carbonate	
JTE-522	Compound M1	selenium	Colon
JTE-522	Compound M1	sulindac	Colon
		sulfone	
JTE-522	Compound M1	Carboplatin	Brain
JTE-522	Compound M1	Goserelin	Prostate
		Acetate	

JTE-522	Compound M1	Ketoconazole	Prostate
JTE-522	Compound M1	Cisplatin	
JTE-522	Compound M2	Anastrozole	Breast
JTE-522	Compound M2	Capecitabine	Breast
JTE-522	Compound M2	Docetaxel	Breast
JTE-522	Compound M2	Gemcitabine	Breast,
			Pancreas
JTE-522	Compound M2	Letrozole	Breast
JTE-522	Compound M2	Megestrol	Breast
JTE-522	Compound M2	Paclitaxel	Breast
JTE-522	Compound M2	Tamoxifen	Breast
JTE-522	Compound M2	. Toremifene	Breast
JTE-522	Compound M2	. Vinorelbine	Breast,
			Lung
JTE-522	Compound M2	? Topotecan	Lung
JTE-522	Compound M2	2 Etoposide	Lung
JTE-522	Compound M2	Fluorouracil	Colon
JTE-522	Compound M2	lrinotecan	Colon,
		(CPT-11)	Bladder
JTE-522	Compound M2	Retinoids	Colon
JTE-522	Compound M2	P. DFMO	Colon
JTE-522	Compound M2	2 Ursodeoxycholi	Colon
		c acid	
JTE-522	Compound M2	calcium	Colon
,		carbonate	
JTE-522	Compound M2	2 selenium	Colon
JTE-522	Compound M2	2 sulindac	Colon
		sulfone	
JTE-522	Compound M2	2 Carboplatin	Brain
JTE-522	Compound M2	2 Goserelin	Prostate
		Acetate	

JTE-522	Compound M2	Ketoconazole	Prostate
JTE-522	Compound M2	Cisplatin	-W.
JTE-522	Compound M3	Anastrozole	Breast
JTE-522	Compound M3	Capecitabine	Breast
JTE-522	Compound M3	Docetaxel	Breast
JTE-522	Compound M3	Gemcitabine	Breast,
			Pancreas
JTE-522	Compound M3	Letrozole	Breast
JTE-522	Compound M3	Megestrol	Breast
JTE-522	Compound M3	Paclitaxel	Breast
JTE-522	Compound M3	Tamoxifen	Breast
JTE-522	Compound M3	Toremifene	Breast
JTE-522	Compound M3	Vinorelbine	Breast,
			Lung
JTE-522	Compound M3	Topotecan	Lung
JTE-522	Compound M3	Etoposide	Lung
JTE-522	Compound M3	Fluorouracil	Colon
JTE-522	Compound M3	Irinotecan	Colon,
		(CPT-11)	Bladder
JTE-522	Compound M3	Retinoids	Colon
JTE-522	Compound M3	DFMO	Colon
JTE-522	Compound M3	Ursodeoxycholi	Colon
		c acid	
JTE-522	Compound M3	calcium	Colon
		carbonate	
JTE-522	Compound M3	selenium	Colon
JTE-522	Compound M3	sulindac	Colon
		sulfone	
JTE-522	Compound M3	Carboplatin	Brain
JTE-522	Compound M3	Goserelin	Prostate
		Acetate	

JTE-522	Compound M3	Ketoconazole	Droctata
			Prostate
JTE-522	Compound M3	Cisplatin	
JTE-522	Compound M4	Anastrozole	Breast
JТE-522	Compound M4	Capecitabine	Breast
JTE-522	Compound M4	Docetaxel	Breast,
			Pancreas
JTE-522	Compound M4	Gemcitabine	Breast
JTE-522	Compound M4	Letrozole	Breast
JTE-522	Compound M4	Megestrol	Breast
JTE-522	Compound M4	Paclitaxel	Breast
JTE-522	Compound M4	Tamoxifen	Breast
JTE-522	Compound M4	Toremifene	Breast,
			Lung
JTE-522	Compound M4	Vinorelbine	Lung
JTE-522	Compound M4	Topotecan	Lung
JTE-522	Compound M4	Etoposide	Colon
JTE-522	Compound M4	Fluorouracil	Colon,
			Bladder
JTE-522	Compound M4	Irinotecan	Colon
		(CPT-11)	
JTE-522	Compound M4	Retinoids	Colon
JTE-522	Compound M4	DFMO	Colon
JTE-522	Compound M4	Ursodeoxycholi	Colon
		c acid	
JTE-522	Compound M4	calcium	Colon
		carbonate	
JTE-522	Compound M4	selenium	Colon
JTE-522	Compound M4	sulindac	Colon
·		sulfone	
JTE-522	Compound M4	Carboplatin	Brain
JTE-522	Compound M4	Goserelin	Prostate
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		Acetate	
JTE-522	Compound M4	Ketoconazole	Prostate
JTE-522	Compound M4	Cisplatin	
JTE-522	Compound M5	Anastrozole	Breast
JTE-522	Compound M5	Capecitabine	Breast
JTE-522	Compound M5	Docetaxel	Breast,
			Pancreas
JTE-522	Compound M5	Gemcitabine	Breast
JTE-522	Compound M5	Letrozole	Breast
JTE-522	Compound M5	Megestrol	Breast
JTE-522	Compound M5	Paclitaxel	Breast
JTE-522	Compound M5	Tamoxifen	Breast
JTE-522	Compound M5	Toremifene	Breast,
			Lung
JTE-522	Compound M5	Vinorelbine	Lung
JTE-522	Compound M5	Topotecan	Lung
JTE-522	Compound M5	Etoposide	Colon
JTE-522	Compound M5	Fluorouracil	Colon,
			Bladder
JTE-522	Compound M5	Irinotecan	Colon
		(CPT-11)	
JTE-522	Compound M5	Retinoids	Colon
JTE-522	Compound M5	DFMO	Colon
JTE-522	Compound M5	Ursodeoxycholi	Colon
		c acid	
JTE-522	Compound M5	calcium	Colon
		carbonate	
JTE-522	Compound M5	selenium	Colon
JTE-522	Compound M5	sulindac	Colon
		sulfone	
JTE-522	Compound M5	Carboplatin	Brain

JTE-522	Compound M5	Goserelin	Prostate
01E-322	compound H3		11056466
		Acetate	
JTE-522	Compound M5	Ketoconazole	Prostate
JTE-522	Compound M5	Cisplatin	
JTE-522	Compound M7	Anastrozole	Breast
JTE-522	Compound M7	Capecitabine	Breast
JTE-522	Compound M7	Docetaxel	Breast,
			Pancreas
JTE-522	Compound M7	Gemcitabine	Breast
JTE-522	Compound M7	Letrozole	Breast
JTE-522	Compound M7	Megestrol	Breast
JTE-522	Compound M7	Paclitaxel	Breast
JTE-522	Compound M7	Tamoxifen	Breast
JTE-522	Compound M7	Toremifene	Breast,
			Lung
JTE-522	Compound M7	Vinorelbine	Lung
JTE-522	Compound M7	Topotecan	Lung
JTE-522	Compound M7	Etoposide	Colon
JTE-522	Compound M7	Fluorouracil	Colon,
			Bladder
JTE-522	Compound M7	Irinotecan	Colon
	•	(CPT-11)	
JTE-522	Compound M7	Retinoids	Colon
JTE-522	Compound M7	DFMO	Colon
JTE-522	Compound M7	Ursodeoxycholi	Colon
		c acid	
JTE-522	Compound M7	calcium	Colon
		carbonate	
JTE-522	Compound M7	selenium	Colon
JTE-522	Compound M7	sulindac	Colon
		sulfone	

JTE-522	Compound M7	Carboplatin	Brain
JTE-522	Compound M7	Goserelin	Prostate
		Acetate	
JTE-522	Compound M7	Ketoconazole	Prostate
JTE-522	Compound M7	Cisplatin	
JTE-522	Bay-12-9566	Anastrozole	Colon
JTE-522	Bay-12-9566	Capecitabine	Brain
JTE-522	Bay-12-9566	Docetaxel	Prostate
JTE-522	Bay-12-9566	Gemcitabine	Prostate
JTE-522	Bay-12-9566	Letrozole	Breast
JTE-522	Bay-12-9566	Megestrol	Breast
JTE-522	Bay-12-9566	Paclitaxel	Breast
JTE-522	Bay-12-9566	Tamoxifen	Breast
JTE-522	Bay-12-9566	Toremifene	Breast
JTE-522	Bay-12-9566	Vinorelbine	Breast,
			Lung
JTE-522	Bay-12-9566	Topotecan	Lung
JTE-522	Bay-12-9566	Etoposide	Lung
JTE-522	Bay-12-9566	Fluorouracil	Colon
JTE-522	Bay-12-9566	Irinotecan	Colon,
	•	(CPT-11)	Bladder
JTE-522	Bay-12-9566	Retinoids	Colon
JTE-522	Bay-12-9566	DFMO	Colon
JTE-522	Bay-12-9566	Ursodeoxycholi	Colon
		c acid	
JTE-522	Bay-12-9566	calcium	Colon
		carbonate	
JTE-522	Bay-12-9566	selenium	Colon
JTE-522	Bay-12-9566	sulindac	Colon
		sulfone	

DTE-522   Bay-12-9566   Goserelin   Acetate	JTE-522	Bay-12-9566	Carboplatin	Brain
JTE-522 Bay-12-9566 Ketoconazole Prostate  JTE-522 Bay-12-9566 Cisplatin  JTE-522 Metastat Anastrozole Breast  JTE-522 Metastat Capecitabine Breast  JTE-522 Metastat Docetaxel Breast  JTE-522 Metastat Gemcitabine Breast,  Pancreas  JTE-522 Metastat Letrozole Breast  JTE-522 Metastat Megestrol Breast  JTE-522 Metastat Paclitaxel Breast  JTE-522 Metastat Tamoxifen Breast  JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Etoposide Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat DFMO Colon  JTE-522 Metastat Ursodeoxycholi Colon  c acid  JTE-522 Metastat calcium Colon  c arbonate  JTE-522 Metastat selenium Colon  JTE-522 Metastat Selenium Colon	JTE-522	Bay-12-9566	Goserelin	Prostate
JTE-522 Bay-12-9566 Cisplatin  JTE-522 Metastat Anastrozole Breast  JTE-522 Metastat Capecitabine Breast  JTE-522 Metastat Docetaxel Breast  JTE-522 Metastat Gemcitabine Breast,  Pancreas  JTE-522 Metastat Letrozole Breast  JTE-522 Metastat Megestrol Breast  JTE-522 Metastat Paclitaxel Breast  JTE-522 Metastat Tamoxifen Breast  JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Vinorelbine Breast,  Lung  JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon,  (CPT-11) Bladder  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat Calcium Colon  C acid  JTE-522 Metastat Calcium Colon  LTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon			Acetate	
JTE-522 Metastat Anastrozole Breast  JTE-522 Metastat Capecitabine Breast  JTE-522 Metastat Docetaxel Breast  JTE-522 Metastat Gemcitabine Breast  JTE-522 Metastat Letrozole Breast  JTE-522 Metastat Megestrol Breast  JTE-522 Metastat Paclitaxel Breast  JTE-522 Metastat Tamoxifen Breast  JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Vinorelbine Breast  JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon,  (CPT-11) Bladder  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat DFMO Colon  JTE-522 Metastat Calcium Colon  c acid  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon	JTE-522	Bay-12-9566	Ketoconazole	Prostate
JTE-522 Metastat Capecitabine Breast  JTE-522 Metastat Docetaxel Breast  JTE-522 Metastat Gemcitabine Breast,  Pancreas  JTE-522 Metastat Letrozole Breast  JTE-522 Metastat Megestrol Breast  JTE-522 Metastat Paclitaxel Breast  JTE-522 Metastat Tamoxifen Breast  JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Vinorelbine Breast,  Lung  JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Etoposide Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon,  (CPT-11) Bladder  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat Ursodeoxycholi Colon  JTE-522 Metastat Calcium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon	JTE-522	Bay-12-9566	Cisplatin	
JTE-522 Metastat Docetaxel Breast  JTE-522 Metastat Gemcitabine Breast, Pancreas  JTE-522 Metastat Letrozole Breast  JTE-522 Metastat Megestrol Breast  JTE-522 Metastat Paclitaxel Breast  JTE-522 Metastat Tamoxifen Breast  JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Vinorelbine Breast, Lung  JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Etoposide Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon, (CPT-11) Bladder  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat DFMO Colon  JTE-522 Metastat Ursodeoxycholi Colon  JTE-522 Metastat Calcium Colon  c acid  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon	JTE-522	Metastat	Anastrozole	Breast
JTE-522 Metastat Gemcitabine Breast, Pancreas  JTE-522 Metastat Letrozole Breast  JTE-522 Metastat Megestrol Breast  JTE-522 Metastat Paclitaxel Breast  JTE-522 Metastat Tamoxifen Breast  JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Vinorelbine Breast, Lung  JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Etoposide Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon, (CPT-11) Bladder  JTE-522 Metastat DFMO Colon  JTE-522 Metastat Ursodeoxycholi Colon  JTE-522 Metastat Calcium Colon  c acid  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon	JTE-522	Metastat	Capecitabine	Breast
JTE-522 Metastat Letrozole Breast  JTE-522 Metastat Megestrol Breast  JTE-522 Metastat Paclitaxel Breast  JTE-522 Metastat Tamoxifen Breast  JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Etoposide Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon,  (CPT-11) Bladder  JTE-522 Metastat BrMO Colon  JTE-522 Metastat Ursodeoxycholi Colon  JTE-522 Metastat Calcium Colon  c acid  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon	JTE-522	Metastat	Docetaxel	Breast
JTE-522MetastatLetrozoleBreastJTE-522MetastatMegestrolBreastJTE-522MetastatPaclitaxelBreastJTE-522MetastatTamoxifenBreastJTE-522MetastatToremifeneBreastJTE-522MetastatVinorelbineBreast, LungJTE-522MetastatTopotecanLungJTE-522MetastatEtoposideLungJTE-522MetastatFluorouracilColonJTE-522MetastatIrinotecanColon, (CPT-11)BladderJTE-522MetastatRetinoidsColonJTE-522MetastatUrsodeoxycholiColonJTE-522MetastatcacidColonJTE-522MetastatcalciumColoncarbonateColoncarbonateJTE-522MetastatseleniumColonJTE-522MetastatseleniumColonJTE-522MetastatseleniumColon	JTE-522	Metastat	Gemcitabine	Breast,
JTE-522 Metastat Paclitaxel Breast  JTE-522 Metastat Paclitaxel Breast  JTE-522 Metastat Tamoxifen Breast  JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Vinorelbine Breast,  Lung  JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Etoposide Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon,  (CPT-11) Bladder  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat DFMO Colon  JTE-522 Metastat Ursodeoxycholi Colon  JTE-522 Metastat Calcium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon				Pancreas
JTE-522 Metastat Paclitaxel Breast  JTE-522 Metastat Tamoxifen Breast  JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Vinorelbine Breast,  Lung  JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Etoposide Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon,  (CPT-11) Bladder  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat DFMO Colon  JTE-522 Metastat Ursodeoxycholi Colon  C acid  JTE-522 Metastat Calcium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon  JTE-522 Metastat Selenium Colon	JTE-522	Metastat	Letrozole	Breast
JTE-522 Metastat Tamoxifen Breast  JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Vinorelbine Breast,  Lung  JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Etoposide Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon,  (CPT-11) Bladder  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat DFMO Colon  JTE-522 Metastat Ursodeoxycholi Colon  c acid  JTE-522 Metastat calcium Colon  carbonate  JTE-522 Metastat selenium Colon  JTE-522 Metastat selenium Colon	JTE-522	Metastat	Megestrol	Breast
JTE-522 Metastat Toremifene Breast  JTE-522 Metastat Vinorelbine Breast, Lung  JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Etoposide Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon, (CPT-11) Bladder  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat DFMO Colon  JTE-522 Metastat Ursodeoxycholi Colon  C acid  JTE-522 Metastat calcium Colon  C arbonate  JTE-522 Metastat selenium Colon  JTE-522 Metastat selenium Colon	JTE-522	Metastat	Paclitaxel	Breast
JTE-522 Metastat Vinorelbine Breast, Lung  JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Etoposide Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon, (CPT-11) Bladder  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat DFMO Colon  JTE-522 Metastat Ursodeoxycholi Colon  c acid  JTE-522 Metastat calcium Colon  carbonate  JTE-522 Metastat selenium Colon  JTE-522 Metastat selenium Colon	JTE-522	Metastat	Tamoxifen	Breast
JTE-522 Metastat Topotecan Lung  JTE-522 Metastat Etoposide Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon,	JTE-522	Metastat	Toremifene	Breast
JTE-522MetastatTopotecanLungJTE-522MetastatEtoposideLungJTE-522MetastatFluorouracilColonJTE-522MetastatIrinotecanColon, (CPT-11)JTE-522MetastatRetinoidsColonJTE-522MetastatDFMOColonJTE-522MetastatUrsodeoxycholiColonCacidColoncacidJTE-522MetastatcalciumColonJTE-522MetastatseleniumColonJTE-522MetastatsulindacColon	JTE-522	Metastat	Vinorelbine	Breast,
JTE-522 Metastat Etoposide Lung  JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon,				Lung
JTE-522 Metastat Fluorouracil Colon  JTE-522 Metastat Irinotecan Colon,	JTE-522	Metastat	Topotecan	Lung
JTE-522 Metastat Irinotecan Colon,  (CPT-11) Bladder  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat DFMO Colon  JTE-522 Metastat Ursodeoxycholi Colon  c acid  JTE-522 Metastat calcium Colon  carbonate  JTE-522 Metastat selenium Colon  JTE-522 Metastat selenium Colon  Colon  Colon  Colon  Colon  Colon  Colon  Colon  Colon  Colon  Colon  Colon	JTE-522	Metastat	Etoposide	Lung
(CPT-11) Bladder  JTE-522 Metastat Retinoids Colon  JTE-522 Metastat DFMO Colon  JTE-522 Metastat Ursodeoxycholi Colon  c acid  JTE-522 Metastat calcium Colon  carbonate  JTE-522 Metastat selenium Colon  JTE-522 Metastat selenium Colon	JTE-522	Metastat	Fluorouracil	Colon
JTE-522MetastatRetinoidsColonJTE-522MetastatDFMOColonJTE-522MetastatUrsodeoxycholiColonC acidColonColonJTE-522MetastatCalciumColonCarbonateColonJTE-522MetastatSeleniumColonJTE-522MetastatSulindacColon	JTE-522	Metastat	Irinotecan	Colon,
JTE-522MetastatDFMOColonJTE-522MetastatUrsodeoxycholiColonC acidc acidColonJTE-522MetastatcalciumColonJTE-522MetastatseleniumColonJTE-522MetastatsulindacColon			(CPT-11)	Bladder
JTE-522 Metastat Ursodeoxycholi Colon   c acid   JTE-522 Metastat calcium Colon   carbonate   JTE-522 Metastat selenium Colon   JTE-522 Metastat sulindac Colon	JTE-522	Metastat	Retinoids	Colon
C acid  JTE-522 Metastat calcium Colon carbonate  JTE-522 Metastat selenium Colon  JTE-522 Metastat sulindac Colon	JTE-522	Metastat	DFMO	Colon
JTE-522Metastatcalcium carbonateColonJTE-522MetastatseleniumColonJTE-522MetastatsulindacColon	JTE-522	Metastat	Ursodeoxycholi	Colon
carbonate  JTE-522 Metastat selenium Colon  JTE-522 Metastat sulindac Colon			c acid	
JTE-522MetastatseleniumColonJTE-522MetastatsulindacColon	JTE-522	Metastat	calcium	Colon
JTE-522 Metastat sulindac Colon			carbonate	,
	JTE-522	Metastat	selenium	Colon
sulfone	JTE-522	Metastat	sulindac	Colon
			sulfone	

JTE-522	Metastat	Carboplatin	Brain
JTE-522	Metastat	Goserelin	Prostate
		Acetate	
JTE-522	Metastat	Ketoconazole	Prostate
JTE-522	Metastat	Cisplatin	:
JTE-522	D-2163	Anastrozole	Breast
JTE-522	D-2163	Capecitabine	Breast
JTE-522	D-2163	Docetaxel	Breast
JTE-522	D-2163	Gemcitabine	Breast,
			Pancreas
JTE-522	D-2163	Letrozole	Breast
JTE-522	D-2163	Megestrol	Breast
JTE-522	D-2163	Paclitaxel	Breast
JTE-522	D-2163	Tamoxifen	Breast
JTE-522	D-2163	Toremifene	Breast
JTE-522	D-2163	Vinorelbine	Breast,
			Lung
JTE-522	D-2163	Topotecan	Lung
JTE-522	D-2163	Etoposide	Lung
JTE-522	D-2163	Fluorouracil	Colon
JTE-522	D-2163	Irinotecan	Colon,
		(CPT-11)	Bladder
JTE-522	D-2163	Retinoids	Colon
JTE-522	D-2163	DFMO	Colon
JTE-522	D-2163	Ursodeoxycholi	Colon
		c acid	
JTE-522	D-2163	calcium	Colon
		carbonate	
JTE-522	D-2163	selenium	Colon
JTE-522	D-2163	sulindac	Colon
		sulfone	

JTE-522 D-2163 Goserelin Prostat Acetate	e
500	
JTE-522 D-2163 Ketoconazole Prostat	e
JTE-522 D-2163 Cisplatin	
JTE-522 D-1927 Anastrozole Breast	
JTE-522 D-1927 Capecitabine Breast	
JTE-522 D-1927 Docetaxel Breast	
JTE-522 D-1927 Gemcitabine Breast,	,
Pancrea	as
JTE-522 D-1927 Letrozole Breast	
JTE-522 D-1927 Megestrol Breast	
JTE-522 D-1927 Paclitaxel Breast	
JTE-522 D-1927 Tamoxifen Breast	
JTE-522 D-1927 Toremifene Breast	
JTE-522 D-1927 Vinorelbine Breast,	
Lung	
JTE-522 D-1927 Topotecan Lung	
JTE-522 D-1927 Etoposide Lung	
JTE-522 D-1927 Fluorouracil Colon	
JTE-522 D-1927 Irinotecan Colon,	
(CPT-11) Bladder	•
JTE-522 D-1927 Retinoids Colon	
JTE-522 D-1927 DFMO Colon	
JTE-522 D-1927 Ursodeoxycholi Colon	
c acid	
JTE-522 D-1927 calcium Colon	
carbonate	,
JTE-522 D-1927 selenium Colon	
JTE-522 D-1927 sulindac Colon	
sulfone	

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JTE-522	D-1927	Carboplatin	Brain
JTE-522	D-1927	Goserelin	Prostate
		Acetate	
JTE-522	D-1927	Ketoconazole	Prostate
JTE-522	D-1927	Cisplatin	

Further examples of combinations are listed in Table No 24, below.

Table No. 24.. Further examples of combination therapies

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COX-2	MMP	3mtinoenlostis	~~ 31 ~~ 11 ~~
		Antineoplastic	Indication
Inhibitor	Inhibitor	Agent	
Celecoxib	Compound M1	Doxorubicin and	Breast
		Cyclophasphamide	
Celecoxib	Compound M1	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
Celecoxib	Compound M1	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Celecoxib	Compound M1	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
Celecoxib	Compound M1	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Celecoxib	Compound M1	Cyclophosphamide,	Breast
		Methotrexate,	

		77	
	5/	Fluorouracil	
Celecoxib	Compound M1	Doxorubicin,	Breast
		Cyclophosphamide,	:
		Methotrexate,	
		Fluorouracil	
Celecoxib	Compound M1	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Celecoxib	Compound M1	Fluorouracil,	Colon
		Levamisole	
Celecoxib	Compound M1	Leucovorin,	Colon
		Fluorouracil	
Celecoxib	Compound M1	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Celecoxib	Compound M1	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
Celecoxib	Compound M1	Etoposide,	Lung
		Carboplatin	
Celecoxib	Compound M1	Etoposide,	Lung
		Cisplatin	
Celecoxib	Compound M1	Paclitaxel,	Lung
		Carboplatin	
Celecoxib	Compound M1	Gemcitabine,	Lung
		Cisplatin	
Celecoxib	Compound M1	Paclitaxel,	Lung
		Cisplatin	
Celecoxib	Compound M2	Doxorubicin and	Breast
		Cyclophasphamide	
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Coloration	Company 2 300	Oral pala 2-3	Descrit
Celecoxib	Compound M2	Cyclophosphamide,	breast
		Doxorubicin, and	
		Fluorouracil	
Celecoxib	Compound M2	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Celecoxib	Compound M2	Mitoxantrone, Flou	Breast
		rouracil and	į
		Leucovorin	
Celecoxib	Compound M2	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Celecoxib	Compound M2	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Celecoxib	Compound M2	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
Celecoxib	Compound M2	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Celecoxib	Compound M2	Fluorouracil,	Colon
		Levamisole	
Celecoxib	Compound M2	Leucovorin,	Colon
		Fluorouracil	
Celecoxib	Compound M2	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
L		<del></del>	

Celecoxib Compound M2 Cyclophosphamide, Lung Doxorubicin, Vincristine  Celecoxib Compound M2 Etoposide, Carboplatin  Celecoxib Compound M2 Etoposide, Cisplatin  Celecoxib Compound M2 Paclitaxel, Carboplatin  Celecoxib Compound M2 Gemcitabine, Cisplatin  Celecoxib Compound M2 Paclitaxel, Cisplatin  Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Pluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Pluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Breast Cyclophosphamide, Breast Br				
Celecoxib Compound M2 Etoposide, Lung Carboplatin  Celecoxib Compound M2 Etoposide, Lung Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Carboplatin  Celecoxib Compound M2 Gemcitabine, Lung Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Cisplatin  Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,	Celecoxib	Compound M2	Cyclophosphamide,	Lung
Celecoxib Compound M2 Etoposide, Lung Carboplatin  Celecoxib Compound M2 Etoposide, Lung Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Carboplatin  Celecoxib Compound M2 Gemcitabine, Lung Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Cisplatin  Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			Doxorubicin,	
Celecoxib Compound M2 Etoposide, Lung Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Carboplatin  Celecoxib Compound M2 Gemcitabine, Lung Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Cisplatin  Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			Vincristine	
Celecoxib Compound M2 Etoposide, Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Carboplatin  Celecoxib Compound M2 Gemcitabine, Lung Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Cisplatin  Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,	Celecoxib	Compound M2	Etoposide,	Lung
Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Carboplatin  Celecoxib Compound M2 Gemcitabine, Lung Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Cisplatin  Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Wethotrexate,			Carboplatin	
Celecoxib Compound M2 Paclitaxel, Lung Carboplatin  Celecoxib Compound M2 Gemcitabine, Lung Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Cisplatin  Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,	Celecoxib	Compound M2	Etoposide,	Lung
Carboplatin  Celecoxib Compound M2 Gemcitabine, Lung Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Cisplatin  Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			Cisplatin	
Celecoxib Compound M2 Gemcitabine, Lung Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Cisplatin  Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,	Celecoxib	Compound M2	Paclitaxel,	Lung
Cisplatin  Celecoxib Compound M2 Paclitaxel, Lung Cisplatin  Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			Carboplatin	
Celecoxib Compound M2 Paclitaxel, Lung Cisplatin  Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,	Celecoxib	Compound M2	Gemcitabine,	Lung
Cisplatin  Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			Cisplatin	
Celecoxib Compound M3 Doxorubicin and Breast Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,	Celecoxib	Compound M2	Paclitaxel,	Lung
Cyclophasphamide  Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			Cisplatin	
Celecoxib Compound M3 Cyclophosphamide, Breast Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,	Celecoxib	Compound M3	Doxorubicin and	Breast
Doxorubicin, and Fluorouracil  Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			Cyclophasphamide	
Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,	Celecoxib	Compound M3	Cyclophosphamide,	Breast
Celecoxib Compound M3 Cyclophosphamide, Breast Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			Doxorubicin, and	
Fluorouracil and Mitoxantrone  Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			Fluorouracil	_
Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,	Celecoxib	Compound M3	Cyclophosphamide,	Breast
Celecoxib Compound M3 Mitoxantrone, Flou Breast rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			Fluorouracil and	
rouracil and Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			Mitoxantrone	
Leucovorin  Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,	Celecoxib	Compound M3	Mitoxantrone, Flou	Breast
Celecoxib Compound M3 Vinblastine, Doxor Breast ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			rouracil and	
ubicin, Thiotepa, and Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			Leucovorin	
and Fluoxymestrone Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,	Celecoxib	Compound M3	Vinblastine,Doxor	Breast
Fluoxymestrone  Celecoxib Compound M3 Cyclophosphamide, Breast  Methotrexate,			ubicin, Thiotepa,	
Celecoxib Compound M3 Cyclophosphamide, Breast Methotrexate,			and	
Methotrexate,			Fluoxymestrone	
	Celecoxib	Compound M3	Cyclophosphamide,	Breast
Fluorouracil			Methotrexate,	
			Fluorouracil	

Celecoxib	Compound M3	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
Celecoxib	Compound M3	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Celecoxib	Compound M3	Fluorouracil,	Colon
		Levamisole	
Celecoxib	Compound M3	Leucovorin,	Colon
		Fluorouracil	
Celecoxib	Compound M3	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Celecoxib	Compound M3	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	-
Celecoxib	Compound M3	Etoposide,	Lung
		Carboplatin	
Celecoxib	Compound M3	Etoposide,	Lung
		Cisplatin	
Celecoxib	Compound M3	Paclitaxel,	Lung
		Carboplatin	
Celecoxib	Compound M3	Gemcitabine,	Lung
		Cisplatin	
Celecoxib	Compound M3	Paclitaxel,	Lung
		Cisplatin	
Celecoxib	Compound M4	Doxorubicin and	Breast
		Cyclophasphamide	
Celecoxib	Compound M4	Cyclophosphamide,	Breast

		Doxorubicin, and	-
		Fluorouracil	
Celecoxib	Compound M4	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Celecoxib	Compound M4	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
Celecoxib	Compound M4	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Celecoxib	Compound M4	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Celecoxib	Compound M4	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
Celecoxib	Compound M4	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Celecoxib	Compound M4	Fluorouracil,	Colon
		Levamisole	
Celecoxib	Compound M4	Leucovorin,	Colon
		Fluorouracil	
Celecoxib	Compound M4	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Celecoxib	Compound M4	Cyclophosphamide,	Lung

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		Doxorubicin,	
		Vincristine	
Celecoxib	Compound M4	Etoposide,	Lung
		Carboplatin	
Celecoxib	Compound M4	Etoposide,	Lung
		Cisplatin	
Celecoxib	Compound M4	Paclitaxel,	Lung
		Carboplatin	
Celecoxib	Compound M4	Gemcitabine,	Lung
		Cisplatin	
Celecoxib	Compound M4	Paclitaxel,	Lung
		Cisplatin	
Celecoxib	Compound M5	Doxorubicin and	Breast
		Cyclophasphamide	
Celecoxib	Compound M5	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
Celecoxib	Compound M5	Cyclophosphamide,	Breast
		Fluorouracil and	•
		Mitoxantrone	
Celecoxib	Compound M5	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
Celecoxib	Compound M5	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Celecoxib	Compound M5	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Celecoxib	Compound M5	Doxorubicin,	Breast

		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
Celecoxib	Compound M5	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Celecoxib	Compound M5	Fluorouracil,	Colon
		Levamisole	
Celecoxib	Compound M5	Leucovorin,	Colon
		Fluorouracil	
Celecoxib	Compound M5	Cyclophosphamide,	Lung
		Doxorubicin,	
F.		Etoposide	
Celecoxib	Compound M5	Cyclophosphamide,	Lung
<u> </u>		Doxorubicin,	
		Vincristine	
Celecoxib	Compound M5	Etoposide,	Lung
		Carboplatin	
Celecoxib	Compound M5	Etoposide,	Lung
		Cisplatin	
Celecoxib	Compound M5	Paclitaxel,	Lung
		Carboplatin	
Celecoxib	Compound M5	Gemcitabine,	Lung
		Cisplatin	
Celecoxib	Compound M5	Paclitaxel,	Lung
		Cisplatin	
Celecoxib	Compound M7	Doxorubicin and	Breast
		Cyclophasphamide	
Celecoxib	Compound M7	Cyclophosphamide,	Breast
!		Doxorubicin, and	
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	<del></del>	Fluorouracil	
Celecoxib	Compound M7	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Celecoxib	Compound M7	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
Celecoxib	Compound M7	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
<u> </u> 		and	
		Fluoxymestrone	
Celecoxib	Compound M7	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Celecoxib	Compound M7	Doxorubicin,	Breast
		Cyclophosphamide,	
	•	Methotrexate,	
		Fluorouracil	
Celecoxib	Compound M7	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Celecoxib	Compound M7	Fluorouracil,	Colon
		Levamisole	
Celecoxib	Compound M7	Leucovorin,	Colon
		Fluorouracil	
Celecoxib	Compound M7	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Celecoxib	Compound M7	Cyclophosphamide,	Lung
		Doxorubicin,	
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		Vincristine	
Celecoxib	Compound M7	Etoposide,	Lung
		Carboplatin	
Celecoxib	Compound M7	Etoposide,	Lung
	•	Cisplatin	
Celecoxib	Compound M7	Paclitaxel,	Lung
		Carboplatin	
Celecoxib	Compound M7	Gemcitabine,	Lung
		Cisplatin	
Celecoxib	Compound M7	Paclitaxel,	Lung
i i		Cisplatin	-
Celecoxib	Bay-12-9566	Doxorubicin and	Breast
		Cyclophasphamide	
Celecoxib	Bay-12-9566	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
Celecoxib	Bay-12-9566	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Celecoxib	Bay-12-9566	Mitoxantrone, Flou	Breast
		rouracil and	
		Leucovorin	
Celecoxib	Bay-12-9566	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Celecoxib	Bay-12-9566	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Celecoxib	Bay-12-9566	Doxorubicin,	Breast
		Cyclophosphamide,	

		Methotrexate,	
		Fluorouracil	
Celecoxib	Bay-12-9566	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Celecoxib	Bay-12-9566	Fluorouracil,	Colon
		Levamisole	
Celecoxib	Bay-12-9566	Leucovorin,	Colon
		Fluorouracil	
Celecoxib	Bay-12-9566	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Celecoxib	Bay-12-9566	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
Celecoxib	Bay-12-9566	Etoposide,	Lung
		Carboplatin	
Celecoxib	Bay-12-9566	Etoposide,	Lung
		Cisplatin	
Celecoxib	Bay-12-9566	Paclitaxel,	Lung
		Carboplatin	
Celecoxib	Bay-12-9566	Gemcitabine,	Lung
		Cisplatin	
Celecoxib	Bay-12-9566	Paclitaxel,	Lung
		Cisplatin	
Celecoxib	Metastat	Doxorubicin and	Breast
		Cyclophasphamide	
Celecoxib	Metastat	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
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Celecoxib	Metastat	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Celecoxib	Metastat	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
Celecoxib	Metastat	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Celecoxib	Metastat	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Celecoxib	Metastat	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
Celecoxib	Metastat	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Celecoxib	Metastat	Fluorouracil,	Colon
		Levamisole	
Celecoxib	Metastat	Leucovorin,	Colon
		Fluorouracil	
Celecoxib	Metastat	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Celecoxib	Metastat	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
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Celecoxib	Metastat	Etoposide,	Lung
		Carboplatin	
Celecoxib	Metastat	Etoposide,	Lung
		Cisplatin	
Celecoxib	Metastat	Paclitaxel,	Lung
		Carboplatin	
Celecoxib	Metastat	Gemcitabine,	Lung
		Cisplatin	1
Celecoxib	Metastat	Paclitaxel,	Lung
		Cisplatin	
Celecoxib	D-2163	Doxorubicin and	Breast
		Cyclophasphamide	
Celecoxib	D-2163	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
Celecoxib	D-2163	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Celecoxib	D-2163	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
Celecoxib	D-2163	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Celecoxib	D-2163	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Celecoxib	D-2163	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
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		Fluorouracil	
Celecoxib	D-2163	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Celecoxib	D-2163	Fluorouracil,	Colon
		Levamisole	
Celecoxib	D-2163	Leucovorin,	Colon
		Fluorouracil	
Celecoxib	D-2163	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Celecoxib	D-2163	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
Celecoxib	D-2163	Etoposide,	Lung
		Carboplatin	
Celecoxib	D-2163	Etoposide,	Lung
		Cisplatin	
Celecoxib	D-2163	Paclitaxel,	Lung
		Carboplatin	
Celecoxib	D-2163	Gemcitabine,	Lung
		Cisplatin	
Celecoxib	D-2163	Paclitaxel,	Lung
		Cisplatin	
Celecoxib	D-1927	Doxorubicin and	Breast
		Cyclophasphamide	
Celecoxib	D-1927	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
Celecoxib	D-1927	Cyclophosphamide,	Breast

		Fluorouracil and	
		Mitoxantrone	
Celecoxib	D-1927	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
Celecoxib	D-1927	Vinblastine, Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Celecoxib	D-1927	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Celecoxib	D-1927	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
Celecoxib	D-1927	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Celecoxib	D-1927	Fluorouracil,	Colon
		Levamisole	
Celecoxib	D-1927	Leucovorin,	Colon
		Fluorouracil	
Celecoxib	D-1927	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Celecoxib	D-1927	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
Celecoxib	D-1927	Etoposide,	Lung
L			

Celecoxib D-1927 Etoposide, Lung Cisplatin Celecoxib D-1927 Paclitaxel, Lung	
Celecoxib D-1927 Paclitaxel, Lung	
Carboplatin	•
Celecoxib D-1927 Gemcitabine, Lung	
Cisplatin	
Celecoxib D-1927 Paclitaxel, Lung	
Cisplatin	
Rofecoxib Compound M1 Doxorubicin and Breast	
Cyclophasphamide	
Rofecoxib Compound M1 Cyclophosphamide, Breast	
Doxorubicin, and	
Fluorouracil	
Rofecoxib Compound M1 Cyclophosphamide, Breast	
Fluorouracil and	
Mitoxantrone	
Rofecoxib Compound M1 Mitoxantrone, Flou Breast	
rouracil and	
Leucovorin	
Rofecoxib Compound M1 Vinblastine, Doxor Breast	
ubicin, Thiotepa,	
and	
Fluoxymestrone	
Rofecoxib Compound M1 Cyclophosphamide, Breast	
Methotrexate,	
Fluorouracil	
Rofecoxib Compound M1 Doxorubicin, Breast	
Cyclophosphamide,	
Methotrexate,	

		D1	
		Fluorouracil	
Rofecoxib	Compound M1	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Rofecoxib	Compound M1	Fluorouracil,	Colon
		Levamisole	
Rofecoxib	Compound M1	Leucovorin,	Colon
		Fluorouracil	
Rofecoxib	Compound M1	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Rofecoxib	Compound M1	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
Rofecoxib	Compound M1	Etoposide,	Lung
		Carboplatin	
Rofecoxib	Compound M1	Etoposide,	Lung
		Cisplatin	
Rofecoxib	Compound M1	Paclitaxel,	Lung
		Carboplatin	
Rofecoxib	Compound M1	Gemcitabine,	Lung
		Cisplatin	
Rofecoxib	Compound M1	Paclitaxel,	Lung
		Cisplatin	
Rofecoxib	Compound M2	Doxorubicin and	Breast
		Cyclophasphamide	
Rofecoxib	Compound M2	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
Rofecoxib	Compound M2	Cyclophosphamide,	Breast

		Fluorouracil and	
		Mitoxantrone	
Rofecoxib	Compound M2	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
Rofecoxib	Compound M2	Vinblastine, Doxor	Breast
·		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Rofecoxib	Compound M2	Cyclophosphamide,	Breast
		Methotrexate,	
-		Fluorouracil	
Rofecoxib	Compound M2	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
Rofecoxib	Compound M2	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Rofecoxib	Compound M2	Fluorouracil,	Colon
		Levamisole	
Rofecoxib	Compound M2	Leucovorin,	Colon
		Fluorouracil	
Rofecoxib	Compound M2	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Rofecoxib	Compound M2	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
Rofecoxib	Compound M2	Etoposide,	Lung

		Constant and a trian	
		Carboplatin	
Rofecoxib	Compound M2	Etoposide,	Lung
		Cisplatin	
Rofecoxib	Compound M2	Paclitaxel,	Lung
		Carboplatin	
Rofecoxib	Compound M2	Gemcitabine,	Lung
		Cisplatin	
Rofecoxib	Compound M2	Paclitaxel,	Lung
		Cisplatin	
Rofecoxib	Compound M3	Doxorubicin and	Breast
		Cyclophasphamide	
Rofecoxib	Compound M3	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
Rofecoxib	Compound M3	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Rofecoxib	Compound M3	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
Rofecoxib	Compound M3	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Rofecoxib	Compound M3	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Rofecoxib	Compound M3	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
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Rofecoxib	Compound M3	Vinblastine,	Breast
		Doxorubicin,	
·		Thiotepa,	ļ
		Fluoxymesterone	
Rofecoxib	Compound M3	Fluorouracil,	Colon
• .		Levamisole	
Rofecoxib	Compound M3	Leucovorin,	Colon
		Fluorouracil	
Rofecoxib	Compound M3	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Rofecoxib	Compound M3	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
Rofecoxib	Compound M3	Etoposide,	Lung
		Carboplatin	
Rofecoxib	Compound M3	Etoposide,	Lung
		Cisplatin	
Rofecoxib	Compound M3	Paclitaxel,	Lung
}		Carboplatin	
Rofecoxib	Compound M3	Gemcitabine,	Lung
		Cisplatin	
Rofecoxib	Compound M3	Paclitaxel,	Lung
		Cisplatin	
Rofecoxib	Compound M4	Doxorubicin and	Breast
		Cyclophasphamide	
Rofecoxib	Compound M4	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
Rofecoxib	Compound M4	Cyclophosphamide,	Breast
		Fluorouracil and	
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		Mitoxantrone	
Rofecoxib	Compound M4	Mitoxantrone, Flou	Breast
		rouracil and	
		Leucovorin	•
Rofecoxib	Compound M4	Vinblastine, Doxor	Breast
		ubicin, Thiotepa,	
		and	
: :		Fluoxymestrone	
Rofecoxib	Compound M4	Cyclophosphamide,	Breast
	,	Methotrexate,	•
		Fluorouracil	
Rofecoxib	Compound M4	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
Rofecoxib	Compound M4	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Rofecoxib	Compound M4	Fluorouracil,	Colon
		Levamisole	
Rofecoxib	Compound M4	Leucovorin,	Colon
		Fluorouracil	
Rofecoxib	Compound M4	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Rofecoxib	Compound M4	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
Rofecoxib	Compound M4	Etoposide,	Lung
		Carboplatin	
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Rofecoxib	Compound M4	Etoposide,	Lung
		Cisplatin	
Rofecoxib	Compound M4	Paclitaxel,	Lung
		Carboplatin	
Rofecoxib	Compound M4	Gemcitabine,	Lung
		Cisplatin	,
Rofecoxib	Compound M4	Paclitaxel,	Lung
		Cisplatin	
Rofecoxib	Compound M5	Doxorubicin and	Breast
		Cyclophasphamide	
Rofecoxib	Compound M5	Cyclophosphamide,	Breast
		Doxorubicin, and	
+		Fluorouracil	
Rofecoxib	Compound M5	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Rofecoxib	Compound M5	Mitoxantrone, Flou	Breast
		rouracil and	
		Leucovorin	
Rofecoxib	Compound M5	Vinblastine, Doxor	Breast
		ubicin, Thiotepa,	
	•	and	
		Fluoxymestrone	
Rofecoxib	Compound M5	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Rofecoxib	Compound M5	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
Rofecoxib	Compound M5	Vinblastine,	Breast

		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
- 6 '1			Colon
Rofecoxib	Compound M5		COTON
		Levamisole	
Rofecoxib	Compound M5	·	Colon
		Fluorouracil	
Rofecoxib	Compound M5	Cyclophosphamide,	Lung
		Doxorubicin,	
1		Etoposide	
Rofecoxib	Compound M5	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
Rofecoxib	Compound M5	Etoposide,	Lung
		Carboplatin	•
Rofecoxib	Compound M5	Etoposide,	Lung
		Cisplatin	
Rofecoxib	Compound M5	Paclitaxel,	Lung
•		Carboplatin	
Rofecoxib	Compound M5	Gemcitabine,	Lung
		Cisplatin	
Rofecoxib	Compound M5	Paclitaxel,	Lung
		Cisplatin	
Rofecoxib	Compound M7	Doxorubicin and	Breast
		Cyclophasphamide	
Rofecoxib	Compound M7	Cyclophosphamide,	Breast
	-	Doxorubicin, and	
		Fluorouracil	
Rofecoxib	Compound M7		Breast
1.01000,120	Joine Juliu 117	Fluorouracil and	<del>-</del>
		Mitoxantrone	

Rofecoxib	Compound M7	Mitoxantrone, Flou	Breast
		rouracil and	
		Leucovorin	
Rofecoxib	Compound M7	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Rofecoxib	Compound M7	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Rofecoxib	Compound M7	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
Rofecoxib	Compound M7	Vinblastine,	Breast
		Doxorubicin,	-
		Thiotepa,	
		Fluoxymesterone	
Rofecoxib	Compound M7	Fluorouracil,	Colon
		Levamisole	
Rofecoxib	Compound M7	Leucovorin,	Colon
		Fluorouracil	
Rofecoxib	Compound M7	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Rofecoxib	Compound M7	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
Rofecoxib	Compound M7	Etoposide,	Lung
		Carboplatin	
Rofecoxib	Compound M7	Etoposide,	Lung

		Cisplatin	
Rofecoxib	Compound M7	Paclitaxel,	Lung
		Carboplatin	
Rofecoxib	Compound M7	Gemcitabine,	Lung
		Cisplatin	
Rofecoxib	Compound M7	Paclitaxel,	Lung
		Cisplatin	
Rofecoxib	Bay-12-9566	Doxorubicin and	Breast
		Cyclophasphamide	
Rofecoxib	Bay-12-9566	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
Rofecoxib	Bay-12-9566	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Rofecoxib	Bay-12-9566	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
Rofecoxib	Bay-12-9566	Vinblastine, Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Rofecoxib	Bay-12-9566	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Rofecoxib	Bay-12-9566	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
Rofecoxib	Bay-12-9566	Vinblastine,	Breast
		Doxorubicin,	

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	`	Thiotepa,	
		Fluoxymesterone	
Rofecoxib	Bay-12-9566	Fluorouracil,	Colon
		Levamisole	<b>4.</b> .
Rofecoxib	Bay-12-9566	Leucovorin,	Colon
		Fluorouracil	
Rofecoxib	Bay-12-9566	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Rofecoxib	Bay-12-9566	Cyclophosphamide,	Lung
<b>,</b>		Doxorubicin,	
		Vincristine	
Rofecoxib	Bay-12-9566	Etoposide,	Lung
		Carboplatin	
Rofecoxib	Bay-12-9566	Etoposide,	Lung
		Cisplatin	
Rofecoxib	Bay-12-9566	Paclitaxel,	Lung
		Carboplatin	
Rofecoxib	Bay-12-9566	Gemcitabine,	Lung
		Cisplatin	
Rofecoxib	Bay-12-9566	Paclitaxel,	Lung
		Cisplatin	
Rofecoxib	Metastat	Doxorubicin and	Breast
		Cyclophasphamide	
Rofecoxib	Metastat	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
Rofecoxib	Metastat	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Rofecoxib	Metastat	Mitoxantrone,Flou	Breast
		· - · · · · · · · · · · · · · · · · · ·	

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		rouracil and	
		Leucovorin	
Rofecoxib	Metastat	Vinblastine, Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Rofecoxib	Metastat	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Rofecoxib	Metastat	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	i
		Fluorouracil	
Rofecoxib	Metastat	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Rofecoxib	Metastat	Fluorouracil,	Colon
		Levamisole	
Rofecoxib	Metastat	Leucovorin,	Colon
	•	Fluorouracil	
Rofecoxib	Metastat	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Rofecoxib	Metastat	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
Rofecoxib	Metastat	Etoposide,	Lung
		Carboplatin	
Rofecoxib	Metastat	Etoposide,	Lung
		Cisplatin	
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Rofecoxib	Metastat	Paclitaxel,	Lung
		Carboplatin	
Rofecoxib	Metastat	Gemcitabine,	Lung
		Cisplatin	
Rofecoxib	Metastat	Paclitaxel,	Lung
·		Cisplatin	They control of the c
Rofecoxib	D-2163	Doxorubicin and	Breast
		Cyclophasphamide	
Rofecoxib	D-2163	Cyclophosphamide,	Breast
1		Doxorubicin, and	
		Fluorouracil	•
Rofecoxib	D-2163	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Rofecoxib	D-2163	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
Rofecoxib	D-2163	Vinblastine, Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
Rofecoxib	D-2163	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
Rofecoxib	D-2163	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
Rofecoxib	D-2163	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	,
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		Fluoxymesterone	
Rofecoxib	D-2163	Fluorouracil,	Colon
		Levamisole	
Rofecoxib	D-2163	Leucovorin,	Colon
		Fluorouracil	
Rofecoxib	D-2163	Cyclophosphamide,	Lung
·		Doxorubicin,	
		Etoposide	
Rofecoxib	D-2163	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
Rofecoxib	D-2163	Etoposide,	Lung
		Carboplatin	
Rofecoxib	D-2163	Etoposide,	Lung
		Cisplatin	
Rofecoxib	D-2163	Paclitaxel,	Lung
		Carboplatin	
Rofecoxib	D-2163	Gemcitabine,	Lung
		Cisplatin	
Rofecoxib	D-2163	Paclitaxel,	Lung
		Cisplatin	
Rofecoxib	D-1927	Doxorubicin and	Breast
		Cyclophasphamide	
Rofecoxib	D-1927	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
Rofecoxib	D-1927	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
Rofecoxib	D-1927	Mitoxantrone, Flou	Breast
		rouracil and	
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		Leucovorin	-
Rofecoxib	D-1927	Vinblastine, Doxor	Breast
		ubicin, Thiotepa,	22 342 3
		and	
		Fluoxymestrone	
Rofecoxib	D 1027		D
ROLECOXID	D-1927	Cyclophosphamide,	Breast
		Methotrexate,	**.
		Fluorouracil	······
Rofecoxib	D-1927	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
	ı	Fluorouracil	
Rofecoxib	D-1927	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
Rofecoxib	D-1927	Fluorouracil,	Colon
		Levamisole	
Rofecoxib	D-1927	Leucovorin,	Colon
		Fluorouracil	
Rofecoxib	D-1927	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
Rofecoxib	D-1927	Cyclophosphamide,	Lung
		Doxorubicin,	ļ
		Vincristine	
Rofecoxib	D-1927	Etoposide,	Lung
		Carboplatin	
Rofecoxib	D-1927	Etoposide,	Lung
		Cisplatin	
Rofecoxib	D-1927	Paclitaxel,	Lung
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		Carboplatin	<del></del>
7.5	D 1007		Tung
Rofecoxib	D-1927	Gemcitabine,	Lung
		Cisplatin	
Rofecoxib	D-1927	Paclitaxel,	Lung
		Cisplatin	
JTE-522	Compound M1	Doxorubicin and	Breast
		Cyclophasphamide	
JTE-522	Compound M1	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
JTE-522	Compound M1	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
JTE-522	Compound M1	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
JTE-522	Compound M1	Vinblastine, Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
JTE-522	Compound M1	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
JTE-522	Compound M1	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
JTE-522	Compound M1	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
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JTE-522 Compound M1 Fluorouracil, Colon  Levamisole  JTE-522 Compound M1 Leucovorin, Colon	
JTE-522 Compound M1 Leucovorin, Colon	
•	
Fluorouracil	
JTE-522 Compound M1 Cyclophosphamide, Lung	
Doxorubicin,	
Etoposide	
JTE-522 Compound M1 Cyclophosphamide, Lung	
Doxorubicin,	
Vincristine	
JTE-522 Compound M1 Etoposide, Lung	î
Carboplatin	
JTE-522 Compound M1 Etoposide, Lung	
Cisplatin	
JTE-522 Compound M1 Paclitaxel, Lung	
Carboplatin	
JTE-522 Compound M1 Gemcitabine, Lung	
Cisplatin	
JTE-522 Compound M1 Paclitaxel, Lung	
Cisplatin	
JTE-522 Compound M2 Doxorubicin and Breast	
Cyclophasphamide	
JTE-522 Compound M2 Cyclophosphamide, Breast	
Doxorubicin, and	
Fluorouracil	
JTE-522 Compound M2 Cyclophosphamide, Breast	
Fluorouracil and	
Mitoxantrone	
JTE-522 Compound M2 Mitoxantrone, Flou Breast	
rouracil and	

		<u> </u>	
		Leucovorin	
JTE-522	Compound M2	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	i
		and	
		Fluoxymestrone	
JTE-522	Compound M2	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
JTE-522	Compound M2	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
JTE-522	Compound M2	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
JTE-522	Compound M2	Fluorouracil,	Colon
		Levamisole	
JTE-522	Compound M2	Leucovorin,	Colon
		Fluorouracil	
JTE-522	Compound M2	Cyclophosphamide,	Lung
		Doxorubicin,	
·		Etoposide	
JTE-522	Compound M2	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
JTE-522	Compound M2	Etoposide,	Lung
		Carboplatin	
JTE-522	Compound M2	Etoposide,	Lung
		Cisplatin	
JTE-522	Compound M2	Paclitaxel,	Lung
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		Carboplatin	
JTE-522	Compound M2		Lung
01E-522	Compound M2	•	bung
		Cisplatin	
JTE-522	Compound M2	Paclitaxel,	Lung
		Cisplatin	
JTE-522	Compound M3	Doxorubicin and	Breast
		Cyclophasphamide	
JTE-522	Compound M3	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
JTE-522	Compound M3	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
JTE-522	Compound M3	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
JTE-522	Compound M3	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
JTE-522	Compound M3	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
JTE-522	Compound M3	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
JTE-522	Compound M3	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	

JTE-522	Compound M3	Fluorouracil,	Colon
		Levamisole	
JTE-522	Compound M3	Leucovorin,	Colon
		Fluorouracil	
JTE-522	Compound M3	Cyclophosphamide,	Lung
4		Doxorubicin,	
		Etoposide	
JTE-522	Compound M3	Cyclophosphamide,	Lung
i		Doxorubicin,	
		Vincristine	
JTE-522	Compound M3	Etoposide,	Lung
		Carboplatin	
JTE-522	Compound M3	Etoposide,	Lung
		Cisplatin	
JTE-522	Compound M3	Paclitaxel,	Lung
		Carboplatin	
JTE-522	Compound M3	Gemcitabine,	Lung
		Cisplatin	
JTE-522	Compound M3	Paclitaxel,	Lung
		Cisplatin	
JTE-522	Compound M4	Doxorubicin and	Breast
		Cyclophasphamide	
JTE-522	Compound M4	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	Ì
JTE-522	Compound M4	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
JTE-522	Compound M4	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
	······································		

JTE-522	Company MA	771-7	D
JTE-522	Compound M4	Vinblastine, Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
JTE-522	Compound M4	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
JTE-522	Compound M4	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	"·
		Fluorouracil	
JTE-522	Compound M4	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
JTE-522	Compound M4	Fluorouracil,	Colon
		Levamisole	
JTE-522	Compound M4	Leucovorin,	Colon
		Fluorouracil	
JTE-522	Compound M4	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
JTE-522	Compound M4	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
JTE-522	Compound M4	Etoposide,	Lung
1		Carboplatin	
JTE-522	Compound M4	Etoposide,	Lung
		Cisplatin	
JTE-522	Compound M4	Paclitaxel,	Lung
		Carboplatin	

JTE-522	Compound M4	Gemcitabine,	Lung
		Cisplatin	_
JTE-522	Compound M4	Paclitaxel,	Lung
		Cisplatin	
JTE-522	Compound M5	Doxorubicin and	Breast
		Cyclophasphamide	,
JTE-522	Compound M5	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
JTE-522	Compound M5	Cyclophosphamide,	Breast
		Fluorouracil and	
·		Mitoxantrone	
JTE-522	Compound M5	Mitoxantrone,Flou	Breast
		rouracil and	:
		Leucovorin	
JTE-522	Compound M5	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
JTE-522	Compound M5	Cyclophosphamide,	Breast
		Methotrexate,	
	·	Fluorouracil	
JTE-522	Compound M5	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
JTE-522	Compound M5	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
JTE-522	Compound M5	Fluorouracil,	Colon
			<del></del>

		Levamisole	
JTE-522	Compound M5	Leucovorin,	Colon
		Fluorouracil	
JTE-522	Compound M5	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
JTE-522	Compound M5	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
JTE-522	Compound M5	Etoposide,	Lung
		Carboplatin	
JTE-522	Compound M5	Etoposide,	Lung
		Cisplatin	
JTE-522	Compound M5	Paclitaxel,	Lung
	_	Carboplatin	
JTE-522	Compound M5	Gemcitabine,	Lung
		Cisplatin	
JTE-522	Compound M5	Paclitaxel,	Lung
		Cisplatin	
JTE-522	Compound M7	Doxorubicin and	Breast
		Cyclophasphamide	
JTE-522	Compound M7	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
JTE-522	Compound M7	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
JTE-522	Compound M7	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
JTE-522	Compound M7	Vinblastine, Doxor	Breast

		ubicin, Thiotepa,	
		and	-
		Fluoxymestrone	
JTE-522	Compound M7	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
JTE-522	Compound M7	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
JTE-522	Compound M7	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
JTE-522	Compound M7	Fluorouracil,	Colon
		Levamisole	
JTE-522	Compound M7	Leucovorin,	Colon
		Fluorouracil	
JTE-522	Compound M7	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
JTE-522	Compound M7	Cyclophosphamide,	Lung
		Doxorubicin,	
		Vincristine	
JTE-522	Compound M7	Etoposide,	Lung
		Carboplatin	
JTE-522	Compound M7	Etoposide,	Lung
		Cisplatin	
JTE-522	Compound M7	Paclitaxel,	Lung
		Carboplatin	
JTE-522	Compound M7	Gemcitabine,	Lung

			<del></del>
		Cisplatin	
JTE-522	Compound M7	Paclitaxel,	Lung
		Cisplatin	
JTE-522	Bay-12-9566	Doxorubicin and	Breast
		Cyclophasphamide	
JTE-522	Bay-12-9566	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
JTE-522	Bay-12-9566	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
JTE-522	Bay-12-9566	Mitoxantrone,Flou	Breast
		rouracil and	
	•	Leucovorin	
JTE-522	Bay-12-9566	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	:
		Fluoxymestrone	
JTE-522	Bay-12-9566	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
JTE-522	Bay-12-9566	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
JTE-522	Bay-12-9566	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
JTE-522	Bay-12-9566	Fluorouracil,	Colon
		Levamisole	

JTE-522	Bay-12-9566	Leucovorin,	Colon
		Fluorouracil	
JTE-522	Bay-12-9566	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	ı
JTE-522	Bay-12-9566	Cyclophosphamide,	Lung
·		Doxorubicin,	
		Vincristine	
JTE-522	Bay-12-9566	Etoposide,	Lung
		Carboplatin	1
JTE-522	Bay-12-9566	Etoposide,	Lung
		Cisplatin	
JTE-522	Bay-12-9566	Paclitaxel,	Lung
		Carboplatin	
JTE-522	Bay-12-9566	Gemcitabine,	Lung
		Cisplatin	•
JTE-522	Bay-12-9566	Paclitaxel,	Lung
·		Cisplatin	
JTE-522	Metastat	Doxorubicin and	Breast
		Cyclophasphamide	
JTE-522	Metastat	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
JTE-522	Metastat	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
JTE-522	Metastat	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
JTE-522	Metastat	Vinblastine, Doxor	Breast
		ubicin, Thiotepa,	
			<del></del>

<del></del>	<del></del>		
		and	
		Fluoxymestrone	
JTE-522	Metastat	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
JTE-522	Metastat	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
JTE-522	Metastat	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
JTE-522	Metastat	Fluorouracil,	Colon
		Levamisole	
JTE-522	Metastat	Leucovorin,	Colon
		Fluorouracil	- - -
JTE-522	Metastat	Cyclophosphamide,	Lung
		Doxorubicin,	:
		Etoposide	
JTE-522	Metastat	Cyclophosphamide,	Lung
	·	Doxorubicin,	
		Vincristine	
JTE-522	Metastat	Etoposide,	Lung
		Carboplatin	
JTE-522	Metastat	Etoposide,	Lung
		Cisplatin	:
JTE-522	Metastat	Paclitaxel,	Lung
		Carboplatin	
JTE-522	Metastat	Gemcitabine,	Lung
		Cisplatin	
			<del></del>

JTE-522	Metastat	Paclitaxel,	Lung
		Cisplatin	
JTE-522	D-2163	Doxorubicin and	Breast
		Cyclophasphamide	
JTE-522	D-2163	Cyclophosphamide,	Breast
		Doxorubicin, and	
		Fluorouracil	
JTE-522	D-2163	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
JTE-522	D-2163	Mitoxantrone, Flou	Breast
		rouracil and	
		Leucovorin	
JTE-522	D-2163	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
		Fluoxymestrone	
JTE-522	D-2163	Cyclophosphamide,	Breast
		Methotrexate,	
		Fluorouracil	
JTE-522	D-2163	Doxorubicin,	Breast
		Cyclophosphamide,	•
		Methotrexate,	
		Fluorouracil	
JTE-522	D-2163	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	
		Fluoxymesterone	
JTE-522	D-2163	Fluorouracil,	Colon
		Levamisole	
JTE-522	D-2163	Leucovorin,	Colon

	<del></del>		
		Fluorouracil	
JTE-522	D-2163	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
JTE-522	D-2163	Cyclophosphamide,	Lung
	-	Doxorubicin,	
		Vincristine	
JTE-522	D-2163	Etoposide,	Lung
		Carboplatin	
JTE-522	D-2163	Etoposide,	Lung
		Cisplatin	
JTE-522	D-2163	Paclitaxel,	Lung
		Carboplatin	
JTE-522	D-2163	Gemcitabine,	Lung
		Cisplatin	
JTE-522	D-2163	Paclitaxel,	Lung
		Cisplatin	
JTE-522	D-1927	Doxorubicin and	Breast
		Cyclophasphamide	
JTE-522	D-1927	Cyclophosphamide,	Breast
		Doxorubicin, and	
	·	Fluorouracil	
JTE-522	D-1927	Cyclophosphamide,	Breast
		Fluorouracil and	
		Mitoxantrone	
JTE-522	D-1927	Mitoxantrone,Flou	Breast
		rouracil and	
		Leucovorin	
JTE-522	D-1927	Vinblastine,Doxor	Breast
		ubicin, Thiotepa,	
		and	
	<del></del>	<del></del>	

		Fluoxymestrone	
JTE-522	D-1927	Cyclophosphamide,	Breast
JTE-522	D-1927		breasc
		Methotrexate,	
		Fluorouracil	·
JTE-522	D-1927	Doxorubicin,	Breast
		Cyclophosphamide,	
		Methotrexate,	
		Fluorouracil	
JTE-522	D-1927	Vinblastine,	Breast
		Doxorubicin,	
		Thiotepa,	·
		Fluoxymesterone	
JTE-522	D-1927	Fluorouracil,	Colon
		Levamisole	
JTE-522	D-1927	Leucovorin,	Colon
		Fluorouracil	
JTE-522	D-1927	Cyclophosphamide,	Lung
		Doxorubicin,	
		Etoposide	
JTE-522	D-1927	Cyclophosphamide,	Lung
,		Doxorubicin,	
		Vincristine	
JTE-522	D-1927	Etoposide,	Lung
		Carboplatin	
JTE-522	D-1927	Etoposide,	Lung
		Cisplatin	
JTE-522	D-1927	Paclitaxel,	Lung
		Carboplatin	
JTE-522	D-1927	Gemcitabine,	Lung
		Cisplatin	
JTE-522	D-1927	Paclitaxel,	Lung

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### Cisplatin

## Biological Evaluation

### COX-2 Inhibitors

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### 1. Lewis Lung Model:

Mice were injected subcutaneously in the left paw ( 1 x 10<sup>6</sup> tumor cells suspended in 30 % Matrigel) and tumor volume was evaluated using a phlethysmometer twice a week for 30-60 days. Blood was drawn twice during the 10 experiment in a 24 h protocol to assess plasma concentration and total exposure by AUC analysis. data are expressed as the mean +/- SEM. Student's and Mann-Whitney tests were used to assess differences between means using the InStat software package. 15 Celecoxib given in the diet at doses between 160-3200 ppm retarded the growth of these tumors. The inhibitory effect of celecoxib was dose-dependent and ranged from 48 % to 85 % as compared with the control tumors. 20 Analysis of lung metastasis was done in all the animals by counting metastasis in a stereomicroscope and by histochemical analysis of consecutive lung sections. Celecoxib did not affect lung metastasis at the lower dose of 160 ppm, however surface metastasis was reduced 25 by more than 50 % when given at doses between 480-3200 In addition, histopathological analysis revealed

that celecoxib dose-dependently reduced the size of the

metastasic lesions in the lung.

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### 2. HT-29 Model:

Mice were injected subcutaneously in the left paw (1 x 10<sup>6</sup> tumor cells suspended in 30 % Matrigel) and 5 tumor volume was evaluated using a phlethysmometer twice a week for 30-60 days. Implantation of human colon cancer cells (HT-29) into nude mice produces tumors that will reach 0.6-2 ml between 30-50 days. Blood was drawn twice during the experiment in a 24 h protocol to assess plasma concentration and total exposure by AUC analysis. The data are expressed as the mean +/- SEM. Student's and Mann-Whitney tests were used to assess differences between means using the InStat software package.

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A. Mice injected with HT-29 cancer cells were 15 treated with cytoxin i.p at doses of 50 mg/kg on days 5,7 and 9 in the presence or absence of celecoxib in the diet. The efficacy of both agents were determined by measuring tumor volume. Treatment using a celecoxib related COX-2 inhibitor (SC-58236) reduced tumor volume 20 by 89 %. In the same assay, indomethacin given at near the maximum tolerated dose of 2 mg/kg/day in the drinking water inhibited tumor formation by 77%. Moreover, the COX-2 selective inhibitor completely inhibited the formation of lung metastasis while the 25 non-selective NSAID indomethacin was ineffective. The results from these studies demonstrate that celecoxib administered in the diet to tumor bearing mice can delay the growth of tumors and metastasis when administered as 30 sole therapy. Moreover, a positive benefit is observed when celecoxib is administered in combination with a cytotoxic agent such as cyclophosphamide.

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B. In a second assay, mice injected with HT-29 cancer cells were treated with 5-FU on days 12 through 15. Mice injected with HT-29 cancer cells were treated with 5-FU i.p at doses of 50 mg/kg on days 12, 13, 14, and 15 in the presence or absence of celecoxib in the diet. The efficacy of both agents were determined by measuring tumor volume. Treatment using a celecoxib reduced tumor volume by 68 %. In the same assay, 5-FU decreased tumor volume by 61%. Further, the combination of celecoxib and 5-FU decreased tumor volume by 83%.

C. In a third assay, mice injected with HT-29 colon cancer cells were treated with 5-FU i.p 50 mg/kg on days 14 through 17 in the presence or absence of celecoxib (1600ppm) and valdecoxib (160 ppm) in the diet. efficacy of both agents were determined by measuring tumor volume. Treatment with 5-FU resulted in a 35% reduction in tumor voloume. Treatment with celecoxib and valdecoxib reduced tumor volume by 52 % and 69 %, respectively. In the same assay, the combination of 5-20 FU and celecoxib decreased tumor volume by 72 % while the combination of 5-FU and valdecoxib decreased tumor volume by 74b % (Table 25).

Table 25. Tumor Volume Effect of Celecoxib and 25 Valdecoxib alone and in combination with 5-Fluorouracil.

Days	Vehicle	5FU	celec-	celec-	valdec-	valdec-
		50mpk	oxib	oxib	oxib	oxib
			160ppm	160ppm	160ppm	160ppm/
				/5 <b>F</b> U		5FU
				50mpk		50mpk

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11	0.04	0.05	0.05	0.05	0.06	0.06
14	0.13	0.12	0.13	0.13	0.13	0.13
18	0.19	0.16	0.17	0.14	0.17	0.16
21	0.23	0.21	0.2	0.17	0.2	0.19
28	0.38	0.3	0.25	0.22	0.25	0.21
35	0.62	0.46	0.35	0.28	0.32	0.29
42	1.01	0.68	0.52	0.32	0.36	0.31

Volume (ml)

D. In a fourth assay, mice injected with HT-29 colon cancer cells were treated with celecoxib (10, 40 or 160 ppm) in the diet beginning at day 10. An approximate dose dependent effect was observed. (Table 26).

Table 26. Celecoxib Inhibitis HT-29 Human Colon Carcinoma

Days	vehicle	10 ppm	40 ppm	160 ppm
14	0.114	0.124	0.125	0.120
22	0.25	0.25	0.19	0.14
28	0.45	0.36	0.27	0.21
35	0.79	0.57	0.4	0.3
42	1.38	0.89	0.68	0.49
50	1.9	1.49	1.04	0.8

10 Volume (ml)

## MMP Inhibitors

- 1. Pancreatic Cell (PC-3) Model:
- In this study, the test groups were a vehicle control, Compound M14, Compound M14 with cisplatin and cisplatin alone with n=10 for each group. The tumors

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were measured with a caliper and the volume calculated using the formula for the volume of an elipsoid. cisplatin dose was 10 mpk administered by the intraperitonal route on day 8 post injecion of tumor 5 cells Compound M14, 50 mpk, was first administered about 6:00 pm the evening of the same day that the tumor cells were injected in the morning. The same dose of Compound M14 was administered bid for each following day. Tumor volume (mm³) was measured on day 25. The data below clearly show an improved response with the combination of the MMP inhibitor and cisplatin.

PC3 Model MMP Inhibitor						
Combination	Combination Study Results					
Agent Administered	Tumor Volume at Day 25					
PC3 Model	(mm³)					
	·					
vehicle	860					
cisplatin	630					
<b>020F</b> 233						
Compound M14	480					
•						
Compound M14	110					
_	210					
with cisplatin						
	<u> </u>					

## 2. Breast Tumor Model:

This study was carried out essentially as PC-3 model. MX-1 breast tumor pieces were implanted (with a trocar) into nude mice with n=10 per group. Dosing with Compound M14(10 mpk or 50 mpk, PO bid) was initiated when the tumors reached a size of 60-120 mg. Dosing was continued for 26 days. Taxol was administered at a dose of 9 mpk for the first five days following the start of dosing by the interperitonal route. The tumors were measured using a caliper and the volume calculated using the formula for the volume of an elipsoid. The results tabulated below clearly show an improved response with combination therapy. An improved response is obtained with lower doses Compound M14.

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MX-1 Model MMP Inhibitor  Combination Study Results				
Agent Administered Tumor Volume at Day 25 (mm³)				
vehicle	1920			
taxol	1280			
Compound M14 @ 10 mpk	960			

Compound M14	1260
@ 50 mpk	
Compound M14 @ 50 mpk +	480
taxol @ 9 mpk	
Compound M14 @ 10 mpk +	240
taxol @ 9 mpk	

# 3. MX-1 Adjuvant Model:

Mice were implanted with MX-1 tumors and allowed to grow to 50 - 100 mm3. The animals were dosed with cyclophosphamide ( 100 or 80 mpk). This was considered Day 1. Two weeks later the animals were pair matched after tumor regression and dosing BID with the MMPI was begun until the end of the experiment. Tumors were measured weekly. The endpoint for the study was a final tumor size of 1.5 g.

	Cycloph-	MMPI		MMPI	MDS	sem
	osfamide			Dose		
	Dose			(mpk)		
	(mpk)					
saline					23.9	1.3
cyclophosphamide	100				39.5	1.2
cyclophosphamide	80				37.2	1.5
cyclophosphamide	100	Compound	M14	200	52.7	2.9
cyclophosphamide	100	Compound	M14	50	43.7	1.6
cyclophosphamide		Compound	M14	200	53.9	2.9
cyclophosphamide	80	Compound	M14	50	44.2	1.8

MDS = mean days to tumor weight of 1.5 g

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### 4. MX-1 breast tumor with taxol:

Mice were implanted with MX-1 tumors and allowed to grow to 50 - 100 mg. The animals were pair matched and this was considered Day 1. Treatment with MMPI was begun BID on Day 1 until the end of the experiment. Taxol was injected IP (15 or 9 mpk) QD for 5 days (days 1 -5). Tumors were measured weekly until an endpoint of 1.5 g was reached.

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	Taxol	MMPI	MMPI	MDS	sem
	1	MALI		MDS	Sem
	Dose		Dose		•
	(mpk)		(mpk)		
vehicle				25.3	0.8
mmpi		Compound	100	32.2	2.8
		M14			
mmpi	· -	Compound	20	34.7	3
		M14			
taxol + mmpi	18	Compound		56	11
_		M14			
taxol + mmpi	9	Compound		30.1	1.8
		M14			
taxol + mmpi	18	Compound	100	61	
		M14			
taxol + mmpi	9	Compound	100	46.7	3.7
_		M14			
taxol + mmpi	18	Compound	20	59.3	7
_		M14			
taxol + mmpi	9	Compound	20	39.3	1.9
		M14			

MDS = 1.5 g

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### 15 5. SK-mes tumor with Taxol

Mice were implanted with SK-mes tumors and allowed to grow to 50 - 100 mg. The animals were pair matched and this was considered Day 1. Treatment with MMPI was begun BID on Day 1 until the end of the experiment.

Taxol was injected IP (18 or 9 mpk) QD for 5 days (days)

1 -5). Tumors were measured weekly until an endpoint of 1.0 g was reached.

	Taxol	MMPI	MMPI	MDS	sem
	Dose		Dose		
	(mpk)		(mpk)		
vehicle				21.2	2.1
iqmm		Compound M14	100	24.7	1.6
mmpi		Compound M14	20	18	1.1
taxol	18			31.5	2.4
taxol	9			26.1	2.3
taxol + mmpi	18	Compound M14	100	43	4
taxol + mmpi	9	Compound M14	100	34.8	1.9
taxol + mmpi	18	Compound M14	20	39.5	3.6
taxol + mmpi	9	Compound M14	20	34.1	5.7

MDS = 1.0 g

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## 5 6. HT-29 tumor with Irinotecan

Mice were implanted with HT-29 tumors and allowed to grow to 50 - 100 mg. The animals were pair matched and this was considered Day 1. Treatment with MMPI was begun BID on Day 1 until the end of the experiment.

Irinotecan was injected IP (100 or 50 mpk) QD for 5 days (days 1-5). Tumors were measured weekly until an endpoint of 1.0 g was reached.

	Irinotecan	MMPI	MMPI	MDS	SEM
	Dose	<b>-</b>	Dose		
	(mpk)		(mpk)		
vehicle				36.4	4.3
mmpi		Compound	100	37.9	5.0
		M14			
mmpi		Compound	20	36	4.2
		M14			
Irinotecan	100			36.7	2.6
Irinotecan	50			38.1	3.0
Irinotecan +	100	Compound	100	51.4	4.4

mmpi		M14			
Irinotecan +	50	Compound M14	100	44.4	4.0
Irinotecan +	100	Compound M14	20	40.6	4.7
Irinotecan +	50	Compound M14	20	36.1	3.0

MDS = 1.0 g

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## What is claimed is:

- A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to 5 said mammal a therapeutically-effective amount of a combination of a cyclooxygenase-2 inhibitor, a matrix metalloproteinase inhibitor, and an antineoplastic agent, wherein said antineoplastic agent is selected from the group consisting of anastrozole, calcium 10 carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-461, docetaxel, doxorubicin, etoposide, fluorouracil (5-FU), fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, 15 paclitaxel, raloxifene, retinoic acid, tamoxifen, thiotepa, topotecan, toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone, exemestane and eflornithine (DFMO). 20
  - 2. The method of Claim 1 wherein the combination is administered in a sequential manner.
- 25 3, The method of Claim 1 wherein the combination is administered in a substantially simultaneous manner.
  - 4. The method of Claim 1 wherein the antineoplastic agent is capecitabine.

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- 5. The method of Claim 1 wherein the antineoplastic agent is carboplatin.
- 6. The method of Claim 1 wherein the antineoplastic agent is cisplatin.
  - 7. The method of Claim 1 wherein the antineoplastic agent is Cell Pathways CP-461.
- 10 8. The method of Claim 1 wherein the antineoplastic agent is docetaxel.
  - 9. The method of Claim 1 wherein the antineoplastic agent is doxorubicin.

15

- 10. The method of Claim 1 wherein the antineoplastic agent is etoposide.
- 11. The method of Claim 1 wherein the 20 antineoplastic agent is fluoxymestrine.
  - 12. The method of Claim 1 wherein the antineoplastic agent is gemcitabine.
- 25 13. The method of Claim 1 wherein the antineoplastic agent is goserelin.
  - 14. The method of Claim 1 wherein the antineoplastic agent is irinotecan.

30

15. The method of Claim 1 wherein the antineoplastic agent is ketoconazole.

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- 16. The method of Claim 1 wherein the antineoplastic agent is letrozol.
- 5 17. The method of Claim 1 wherein the antineoplastic agent is leucovorin.
  - 18. The method of Claim 1 wherein the antineoplastic agent is levamisole.

10

- 19. The method of Claim 1 wherein the antineoplastic agent is megestrol.
- 20. The method of Claim 1 wherein the antineoplastic agent is mitoxantrone.
  - 21. The method of Claim 1 wherein the antineoplastic agent is paclitaxel.
- 20 22. The method of Claim 1 wherein the antineoplastic agent is raloxifene.
  - 23. The method of Claim 1 wherein the antineoplastic agent is retinoic acid.

25

- 24. The method of Claim 1 wherein the antineoplastic agent is tamoxifen.
- 25. The method of Claim 1 wherein the antineoplastic agent is thiotepa.

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- 26. The method of Claim 1 wherein the antineoplastic agent is topotecan.
- 27. The method of Claim 1 wherein the antineoplastic agent is toremifene.
  - 28. The method of Claim 1 wherein the antineoplastic agent is vinorelbine.
- 10 29. The method of Claim 1 wherein the antineoplastic agent is vinblastine.
  - 30. The method of Claim 1 wherein the antineoplastic agent is vincristine.

15

- 31. The method of Claim 1 wherein the antineoplastic agent is selenium (selenomethionine).
- 32. The method of Claim 1 wherein the 20 antineoplastic agent is sulindac sulfone.
  - 33. The method of Claim 1 wherein the antineoplastic agent is effornithine (DFMO).
- 25 34. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

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5)

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3phenyl-2(5H)-furanone,

5 6)

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

7) N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide,

8)

10

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

9)

$$\begin{array}{c} \text{CI} \\ \\ \text{CI} \\ \\ \text{CI} \\ \end{array}$$

10)

5 11)

6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

12)

10

 ${\tt N-(4-nitro-2-phenoxyphenyl)} \, {\tt methane sulfonamide},$ 

13)

$$CI$$
 $O$ 
 $OC_2H_5$ 
 $CF_3$ 

14)

5

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

15)

10

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

5 17)

4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

18)

10

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

$$H_2N$$
  $CH_3$ 

4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

5 20)

3-(4-fluorophenyl)-4-[4(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)

10

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide,

5 23)

$$H_2N$$
  $S$   $O$   $O$ 

4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

24)

10

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

N-[2-(cyclohexyloxy)-4nitrophenyl]methanesulfonamide,

5 26)

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

27)

10

3-(4-chlorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5 29)

3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl) amino]benzenesulfonamide,

30)

10

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

5 32)

3-[(2,4-dichlorophenyl)thio]-4[(methylsulfonyl)amino]benzenesulfonamide,

33)

10

1-fluoro-4-[2-[4 (methylsulfonyl)phenyl]cyclopenten-1yl]benzene,

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

5 35)

3-[1-[4-(methylsulfonyl)phenyl]-4(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1Himidazol-1-yl]benzenesulfonamide,

5 37)

4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

38)

10

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

$$H_2N$$
  $CF_2H$ 

4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

5 40)

[1,1':2',1"-terphenyl]-4-sulfonamide,

41)

10

4-(methylsulfonyl)-1,1',2],1"-terphenyl,

4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

43)

5

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

44)

10

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

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45)

46)

$$CI$$
 $CF_3$ 
 $CI$ 
 $CF_3$ 

5 47)

$$\begin{array}{c} \text{MeS} \\ \\ \text{SO}_2\text{NH}_2 \\ \\ \text{CH}_3 \end{array} \quad \text{, and} \quad$$

48)

35. The method of Claim 1 wherein the

10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4- (methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

- 36. The method of Claim 1 wherein the cycloo7xygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.
- 37. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

- 38. The method of Claim 1 wherein the
- 10 cyclooxygenase-2 inhibitor is

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

15 39. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

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40. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is N-[[4-(5-methyl-3phenylisoxazol-4yl]phenyl]sulfonyl]propanamide.

The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1Hpyrazole-1-yl]benzenesulfonamide.

- The method of Claim 1 wherein the neoplasia is selected from the group consisting of lung cancer, 10 breast cancer, gastrointestinal cancer, bladder cancer, head and neck cancer and cervical cancer.
- The method of Claim 1 wherein the neoplasia is selected from the group consisting of acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid 15 cycstic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, 20 cavernous, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma,
- 25 germ cell tumors, glioblastoma, glucagonoma,

hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular 10 melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, 15 sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous 20 carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

44. The method of Claim 1 wherein the matrix

metalloproteinase inhibitor is selected from compounds,
and their pharmaceutically acceptable salts thereof, of
the group consisting of:

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

2)

5

1-cyclopropyl-N-hydroxy-4-[[4-[4-10 (trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

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3)

5

10

HON SON CF3

HCl N

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

HCl N

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide,

6)

5

10

15

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

7)

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

9)

5

British Biotech BB-2516 (Marimastat), N4-[2,2-10 dimethyl- 1-[(methylamino)carbonyl]propyl]N1,2 -dihydroxy-3 (2-methylpropyl)-, [2S[N4(R\*),2R\*,3S\*]]-),

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10)

Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]- 4-yl)oxy]-2[(phenylthio)methyl]butanoic acid,

11)

5

15

Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2

dimethyl-4-[[4-(4pyridinyloxy)phenyl]sulfonyl] 3thiomorpholinecarboxamide,

- 12) CollaGenex Pharmaceuticals CMT-3 (Metastat),
  6-demethyl-6-deoxy-4dedimethylaminotetracycline,
- 13) Chiroscience D-2163, 2- [1S- ([(2R,S)-acetylmercapto-5-phthalimido]pentanoyl-L-leucyl)amino-3-methylbutyl]imidazole,

N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

15)

5

10

15

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4 (trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

16)

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinearboxamide,

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17)

1-cyclopropyl-N-hydroxy-4-[[4-[4(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

18)

5

10

15

4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

19)

4-[[4-(4-

chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide,

N-hydroxy-4-[[4-(4-

methoxyphenoxy)phenyl)sulfonyl]-1-(2-

propynyl) -4-piperidinecarboxamide,

21)

5

10

1-cyclopropyl-4-[[4-[(4-

fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-

4-piperidinecarboxamide,

22)

1-cyclopropyl-N-hydroxy-4-[[4-

(phenylthio)phenyl]sulfonyl]-4-

15 piperidinecarboxamide,

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23)

-344-

tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide, and

24)

5

10

tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2Hpyran-4-carboxamide.

45. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride.

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46. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride.

47. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

10

5

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride. 10

48. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

49. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide.

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50. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

51. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

10

15

5

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

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52. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

5

15

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

53. The method of Claim 1 wherein the matrix 10 metalloproteinase inhibitor is

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-).

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54. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

5

Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]- 4-yl)oxy]-2[(phenylthio)methyl]butanoic acid.

55. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

10

20

Agouron Pharmaceuticals AG-3340, N-hydroxy-

2,2-dimethyl-4-[[4-(4-

pyridinyloxy)phenyl]sulfonyl]- 3thiomorpholinecarboxamide.

56. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is CollaGenex Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-dedimethylaminotetracycline.

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57. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is Chiroscience D-2163, 2-[1S-([(2R,S)-acetylmercapto-5-phthalimido]pentanoyl-L-leucyl)amino-3-methylbutyl]imidazole.

5

- A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to said mammal a therapeutically-effective amount of a 10 combination of radiation, a cyclooxygenase-2 inhibitor, a matrix metalloproteinase inhibitor, and an antineoplastic agent, wherein said antineoplastic agent is selected from the group consisting of anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-461, docetaxel, doxorubicin, etoposide, 15 fluorouracil (5-FU), fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid, tamoxifen, thiotepa, topotecan, toremifene, vinorelbine, 20 vinblastine, vincristine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone, exemestane and eflornithine (DFMO).
- 59. The method of Claim 58 wherein the combination is administered in a sequential manner.
  - 60. The method of Claim 58 wherein the combination is administered in a substantially simultaneous manner.

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- 61. The method of Claim 58 wherein the antineoplastic agent is capecitabine.
- 62. The method of Claim 58 wherein the antineoplastic agent is carboplatin.
  - 63. The method of Claim 58 wherein the antineoplastic agent is cisplatin.
- 10 64. The method of Claim 58 wherein the antineoplastic agent is Cell Pathways CP-461.
  - 65. The method of Claim 58 wherein the antineoplastic agent is docetaxel.

15

- 66. The method of Claim 58 wherein the antineoplastic agent is doxorubicin.
- 67. The method of Claim 58 wherein the 20 antineoplastic agent is etoposide.
  - 68. The method of Claim 58 wherein the antineoplastic agent is fluoxymestrine.
- 25 69. The method of Claim 58 wherein the antineoplastic agent is gemcitabine.
  - 70. The method of Claim 58 wherein the antineoplastic agent is goserelin.

30

71. The method of Claim 58 wherein the antineoplastic agent is irinotecan.

- 72. The method of Claim 58 wherein the antineoplastic agent is ketoconazole.
- 5 73. The method of Claim 58 wherein the antineoplastic agent is letrozol.
  - 74. The method of Claim 58 wherein the antineoplastic agent is leucovorin.

10

- 75. The method of Claim 58 wherein the antineoplastic agent is levamisole.
- 76. The method of Claim 58 wherein the antineoplastic agent is megestrol.
  - 77. The method of Claim 58 wherein the antineoplastic agent is mitoxantrone.
- 78. The method of Claim 58 wherein the antineoplastic agent is paclitaxel.
  - 79. The method of Claim 58 wherein the antineoplastic agent is raloxifene.

25

- 80. The method of Claim 58 wherein the antineoplastic agent is retinoic acid.
- 81. The method of Claim 58 wherein the 30 antineoplastic agent is tamoxifen.

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- 82. The method of Claim 58 wherein the antineoplastic agent is thiotepa.
- 83. The method of Claim 58 wherein the 5 antineoplastic agent is topotecan.
  - 84. The method of Claim 58 wherein the antineoplastic agent is toremifene.
- 10 85. The method of Claim 58 wherein the antineoplastic agent is vinorelbine.
  - 86. The method of Claim 58 wherein the antineoplastic agent is vinblastine.

15

- 87. The method of Claim 58 wherein the antineoplastic agent is vincristine.
- 88. The method of Claim 58 wherein the antineoplastic agent is selenium (selenomethionine).
  - 89. The method of Claim 58 wherein the antineoplastic agent is sulindac sulfone.
- 25 90. The method of Claim 58 wherein the antineoplastic agent is effornithine (DFMO).

91. The method of Claim 58 wherein the cyclooxygenase-2 inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

5 1)

$$H_2N$$
 $F$ 
 $O$ 
 $CH_3$ 

JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)2-fluorobenzenesulfonamide,

2)

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine,

3)

2-(3,5-difluorophenyl)-3-4(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

15 4)

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide,

-355-

5)

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3phenyl-2(5H)-furanone,

5 6)

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

7) N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide,

8)

10

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

10)

5 11)

6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

12)

10

N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

-357-

13)

$$CI \xrightarrow{O \\ OC_2H_5}$$

14)

5 3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-

(methylsulfonyl)phenyl]-2(5H)-furanone,

15)

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-

10 oxo-1H-inden-5-yl]methanesulfonamide,

16)

3-(4-chlorophenyl)-4-[4-

(methylsulfonyl)phenyl]-2(3H)-oxazolone,

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17)

4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

5 18)

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

19)

$$H_2N$$
  $O$   $O$   $O$   $O$   $O$ 

10

4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

20)

15

3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone, WO 00/37107 PCT/US99/30776

-359-

21)

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

22)

5

4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide,

23)

$$H_2N$$
  $S$   $CF_3$ 

4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

10

-360-

24)

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

5 25)

N-[2-(cyclohexyloxy)-4nitrophenyl]methanesulfonamide,

26)

10

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

3-(4-chlorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5

28)

3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

10 29)

3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl) amino]benzenesulfonamide,

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30)

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5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3phenoxy-2(5H)-furanone,

31)

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

10 32)

3-[(2,4-dichlorophenyl)thio]-4-

[(methylsulfonyl)amino]benzenesulfonamide,

1-fluoro-4-[2-[4 (methylsulfonyl)phenyl]cyclopenten-1yl]benzene,

34)

5

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

10 35)

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

5 37)

4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

38)

10

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

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39)

$$H_2N$$
  $CF_2H$ 

4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

5 40)

[1,1':2',1"-terphenyl]-4-sulfonamide,

41)

4-(methylsulfonyl)-1,1',2],1"-terphenyl,

4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

43)

5

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

44)

10

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

46)

$$CI$$
 $O$ 
 $CF_3$ 

5 47)

$$\begin{array}{c} \text{MeS} \\ \text{SO}_2\text{NH}_2 \\ \\ \text{CH}_3 \end{array} \quad \text{, and} \quad$$

48)

92. The method of Claim 58 wherein the

10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4- (methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

- 93. The method of Claim 58 wherein the cycloo7xygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.
- 94. The method of Claim 58 wherein the 5 cyclooxygenase-2 inhibitor is

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

95. The method of Claim 58 wherein the 10 cyclooxygenase-2 inhibitor is

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

15 96. The method of Claim 58 wherein the cyclooxygenase-2 inhibitor is

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

- 97. The method of Claim 58 wherein the cyclooxygenase-2 inhibitor is N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide.
- 98. The method of Claim 58 wherein the 5 cyclooxygenase-2 inhibitor is

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide.

- 99. The method of Claim 58 wherein the neoplasia

  10 is selected from the group consisting of lung cancer,
  breast cancer, gastrointestinal cancer, bladder cancer,
  head and neck cancer and cervical cancer.
  - 100. The method of Claim 58 wherein the neoplasia is selected from the group consisting of acral
- lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cycstic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma,
- carcinosarcoma, cavernous, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid,
- 25 Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma,

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Wilm's tumor.

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glucagonoma, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic 'carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular 10 melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal 15 cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, 20 undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and

101. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

5 1)

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

10

15

2)

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

4)

10

5

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide,

6)

5

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-10 (trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide dihydrochloride,

7)

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-15 (trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide dihydrochloride, WO 00/37107 PCT/US99/30776

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8)

5 N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

9)

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]N1,2 -dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-),

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10)

Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'iphenyl]- 4-yl)oxy]-2[(phenylthio)methyl]butanoic acid,

11)

5

15

Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2

dimethyl-4-[[4-(4pyridinyloxy)phenyl]sulfonyl] 3thiomorpholinecarboxamide,

- 12) CollaGenex Pharmaceuticals CMT-3 (Metastat),
  6-demethyl-6-deoxy-4dedimethylaminotetracycline,
- 13) Chiroscience D-2163, 2- [1S- ([(2R,S)acetylmercapto- 5- phthalimido]pentanoyl- Lleucyl)amino- 3- methylbutyl]imidazole,

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14)

N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

15)

5

10

15

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4 (trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

16)

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinearboxamide,

1-cyclopropyl-N-hydroxy-4-[[4-[4(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

18)

5

10

15

4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

19)

4-[[4-(4-

chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide,

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20)

N-hydroxy-4-[[4-(4-

methoxyphenoxy)phenyl)sulfonyl]-1-(2-

propynyl)-4-piperidinecarboxamide,

21)

5

10

1-cyclopropyl-4-[[4-[(4-

fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-

4-piperidinecarboxamide,

22)

1-cyclopropyl-N-hydroxy-4-[[4-

(phenylthio)phenyl]sulfonyl]-4-

15 piperidinecarboxamide,

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23)

tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide, and

24)

5

10

tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2Hpyran-4-carboxamide.

102. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-15 (trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride. -380-

103. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride.

104. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

10

5

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

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105. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

106. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

H-0 10 0 0 CF

10

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide.

107. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

5

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

108. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

10

15

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

109. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

5

15

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

110. The method of Claim 58 wherein the matrix 10 metalloproteinase inhibitor is

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]- N1,2 -dihydroxy-3 (2- methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-).

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111. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

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Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'iphenyl]- 4-yl)oxy]-2-

[(phenylthio)methyl]butanoic acid.

112. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

10

15

20

Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2-dimethyl-4-[[4-(4-

pyridinyloxy)phenyl]sulfonyl]- 3thiomorpholinecarboxamide.

- 113. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is CollaGenex

  Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-dedimethylaminotetracycline.
- 114. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is Chiroscience D-2163, 2-

[1S- ([(2R,S)- acetylmercapto- 5- phthalimido]pentanoyl-L- leucyl)amino- 3- methylbutyl]imidazole.

- 115. A combination comprising a cyclooxygenase-2 inhibitor, a matrix metalloproteinase inhibitor, and an 5 antineoplastic agent, wherein said antineoplastic agent is selected from the group consisting of anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-461, docetaxel, doxorubicin, etoposide, fluorouracil (5-FU), fluoxymestrine, gemcitabine, 10 goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid, tamoxifen, thiotepa, topotecan, toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine), 15 ursodeoxycholic acid, sulindac sulfone, exemestane and eflornithine (DFMO).
- 116. The combination of Claim 115 wherein the

  20 cyclooxygenase-2 inhibitor is selected from compounds,
  and their pharmaceutically acceptable salts thereof, of
  the group consisting of:

1)

25

JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)2-fluorobenzenesulfonamide,

5

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5-chloro-3-(4-(methylsulfonyl)phenyl)-2(methyl-5-pyridinyl)pyridine,

3)
2-(3,5-difluorophenyl)-3-4(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

H<sub>2</sub>NO<sub>2</sub>S CH<sub>3</sub>

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1Hpyrazol-1-yl]-benzenesulfonamide,

5) H<sub>3</sub>CO<sub>2</sub>S

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3phenyl-2(5H)-furanone,

H<sub>2</sub>NO<sub>2</sub>S

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

7) N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide,

8)

5 4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1Hpyrazole-1-yl]benzenesulfonamide,

9)

10)

11)

10

6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

N-(4-nitro-2-phenoxyphenyl) methanesulfonamide,

13)

$$CI$$
 $O$ 
 $OC_2H_5$ 
 $CF_3$ 

14)

5

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

10 15)

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

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16)

3-(4-chlorophenyl)-4-[4(methylsulfonyl)phenyl]-2(3H)-oxazolone,

5 17)

4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

18)

10

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

5 20)

3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)

10

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide,

5 23)

$$H_2N$$

4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

24)

10

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

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25)

N-[2-(cyclohexyloxy)-4nitrophenyl]methanesulfonamide,

5 26)

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

27)

10

3-(4-chlorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

-393-

28)

3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5 29)

3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl) amino]benzenesulfonamide,

30)

10

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,

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31)

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

5 32)

3-[(2,4-dichlorophenyl)thio]-4-

[(methylsulfonyl)amino]benzenesulfonamide,

33)

10

1-fluoro-4-[2-[4(methylsulfonyl)phenyl]cyclopenten-1yl]benzene,

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

5 35)

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

5 37)

4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

38)

10

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

$$H_2N$$
  $CF_2H$ 

4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

5 40)

[1,1':2',1"-terphenyl]-4-sulfonamide,

41)

4-(methylsulfonyl)-1,1',2],1"-terphenyl,

4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

43)

5

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

44)

10

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

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45)

46)

$$CI$$
 $O$ 
 $CF_3$ 

5 47)

$$\begin{array}{c} \text{MeS} \\ \\ \text{SO}_2\text{NH}_2 \\ \\ \text{CH}_3 \end{array} \quad \text{, and} \quad$$

48)

117. The combination of Claim 115 wherein the

10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4- (methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

- 118. The combination of Claim 115 wherein the cycloo7xygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.
- 119. The combination of Claim 115 wherein the cyclooxygenase-2 inhibitor is

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

120. The combination of Claim 115 wherein the 10 cyclooxygenase-2 inhibitor is

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

15 121. The combination of Claim 115 wherein the cyclooxygenase-2 inhibitor is

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

- 122. The combination of Claim 115 wherein the cyclooxygenase-2 inhibitor is N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide.
- 123. The combination of Claim 115 wherein the 5 cyclooxygenase-2 inhibitor is

4-[5-(4-choropheny1)-3-(trifluoromethy1)-1H-pyrazole-1-yl]benzenésulfonamide.

- 124. The combination of Claim 115 wherein the
  10 neoplasia is selected from the group consisting of lung
  cancer, breast cancer, gastrointestinal cancer, bladder
  cancer, head and neck cancer and cervical cancer.
- 125. The combination of Claim 115 wherein the neoplasia is selected from the group consisting of acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cycstic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma,
- 20 carcinosarcoma, cavernous, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid,
- 25 Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma,

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glucagonoma, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, 5 invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, 10 neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal 15 cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, 20 undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

126. The combination of Claim 115 wherein the
25 matrix metalloproteinase inhibitor is selected from
compounds, and their pharmaceutically acceptable salts
thereof, of the group consisting of:

. 1)

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

2)

10

5

1-cyclopropyl-N-hydroxy-4-[[4-[4(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

4)

10

5

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1piperidinyl]sulfonyl]benzamide,

6)

5

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-10 (trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide dihydrochloride,

7)

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-15 (trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide dihydrochloride,

5

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

9)

10

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]- N1,2 -dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-),

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10)

Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]- 4-yl)oxy]-2[(phenylthio)methyl]butanoic acid,

11)

5

15

Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2

dimethyl-4-[[4-(4pyridinyloxy)phenyl]sulfonyl] 3thiomorpholinecarboxamide,

- 12) CollaGenex Pharmaceuticals CMT-3 (Metastat),
  6-demethyl-6-deoxy-4dedimethylaminotetracycline,
- 13) Chiroscience D-2163, 2- [1S- ([(2R,S)acetylmercapto- 5- phthalimido]pentanoyl- Lleucyl)amino- 3- methylbutyl]imidazole,

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14)

N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

15)

. 5

10

15

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4 (trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

16)

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinearboxamide,

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

18)

5

10

15

4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

19)

4-[[4-(4-

chlorophenoxy)phenyl]sulfonyl]tetrahydro-Nhydroxy-2H-pyran-4-carboxamide,

N-hydroxy-4-[[4-(4-

methoxyphenoxy)phenyl)sulfonyl]-1-(2-

propynyl)-4-piperidinecarboxamide,

21)

5

10 .

1-cyclopropyl-4-[[4-[(4-

fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-

4-piperidinecarboxamide,

22)

1-cyclopropyl-N-hydroxy-4-[[4-

(phenylthio)phenyl]sulfonyl]-4-

15 piperidinecarboxamide,

-411-

23)

tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide, and

24)

5

10

tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2Hpyran-4-carboxamide.

127. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-15 (trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride.

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128. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride.

129. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is

10

5

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride. 5

10

130. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

131. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide.

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132. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is

5

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

133. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is

10

15

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

134. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is

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N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

135. The combination of Claim 115 wherein the 10 matrix metalloproteinase inhibitor is

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]N1,2 -dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-).

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136. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is

Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]- 4-yl)oxy]-2-

[(phenylthio)methyl]butanoic acid.

137. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is

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Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxamide.

- 138. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is CollaGenex Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-dedimethylaminotetracycline.
- 139. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is Chiroscience D-

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2163, 2- [1S- ([(2R,S)- acetylmercapto- 5-phthalimido]pentanoyl- L- leucyl)amino- 3-methylbutyl]imidazole.

- 5 140. The method of Claim 1 wherein the antineoplastic agent is anastrozole.
  - 141. The method of Claim 1 wherein the antineoplastic agent is calcium carbonate.

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- 142. The method of claim 1 wherein the antineoplastic agent is exemestane.
- 143. The method of Claim 58 wherein the combination is administered in a sequential manner.
  - 144. The method of Claim 58 wherein the combination is administered in a substantially simultaneous manner.
- 20 145. The method of claim 1 wherein the antineoplastic agent is exemestane.
- 146. A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to said mammal a therapeutically-effective amount of a combination of a cyclooxygenase-2 inhibitor and a matrix metalloproteinase inhibitor, wherein said matrix metalloproteinase inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

2)

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1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

4)

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N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide,

6)

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N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

7)

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

9)

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British Biotech BB-2516 (Marimastat), N4-[2,2-10 dimethyl- 1-[(methylamino)carbonyl]propyl]N1,2 -dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-),

Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]- 4-yl)oxy]-2[(phenylthio)methyl]butanoic acid,

11)

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Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2

dimethyl-4-[[4-(4pyridinyloxy)phenyl]sulfonyl] 3thiomorpholinecarboxamide,

- 12) CollaGenex Pharmaceuticals CMT-3 (Metastat),
  6-demethyl-6-deoxy-4dedimethylaminotetracycline,
- 13) Chiroscience D-2163, 2- [1S- ([(2R,S)acetylmercapto- 5- phthalimido]pentanoyl- Lleucyl)amino- 3- methylbutyl]imidazole,

N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

15)

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N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4 (trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

16)

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinearboxamide,

1-cyclopropyl-N-hydroxy-4-[[4-[4(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

18)

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4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

19)

4-[[4-(4-

chlorophenoxy)phenyl]sulfonyl]tetrahydro-Nhydroxy-2H-pyran-4-carboxamide,

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20)

N-hydroxy-4-[[4-(4-

methoxyphenoxy)phenyl)sulfonyl]-1-(2-

propynyl)-4-piperidinecarboxamide,

21)

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1-cyclopropyl-4-[[4-[(4-

fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-

4-piperidinecarboxamide,

22)

1-cyclopropyl-N-hydroxy-4-[[4-

(phenylthio)phenyl]sulfonyl]-4-

15 piperidinecarboxamide,

-426-

23)

tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide, and

24)

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tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2Hpyran-4-carboxamide.

147. The method of Claim 146 comprising administering to said mammal a therapeutically-effective amount of a combination of an cyclooxygenase-2

- inhibitor, a matrix metalloproteinase inhibitor, and an antineoplastic agent, wherein the antineoplastic agent is selected from the group consisting of anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-461, docetaxel, doxorubicin, etoposide,
- fluorouracil (5-FU), fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid, tamoxifen, thiotepa, topotecan, toremifene, vinorelbine,
- 25 vinblastine, vincristine, selenium (selenomethionine),

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ursodeoxycholic acid, sulindac sulfone and eflornithine (DFMO).

- 148. The method of Claim 146 comprising
  5 administering to said mammal a therapeutically-effective
  amount of a combination of radiation, a cyclooxygenase-2
  inhibitor and a matrix metalloproteinase inhibitor.
- 149. A combination comprising a cyclooxygenase-2

  10 inhibitor and a matrix metalloproteinase inhibitor,
  wherein said matrix metalloproteinase inhibitor is
  selected from compounds, and their pharmaceutically
  acceptable salts thereof, of the group consisting of:

1)

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N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

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2)

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

5 3)

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

4)

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N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

5)

5

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide,

6)

10

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

7)

15

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

5 8)

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

9)

10

15

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]N1,2 -dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-),

10)

Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]- 4-yl)oxy]-2[(phenylthio)methyl]butanoic acid,

5 11)

Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2 dimethyl-4-[[4-(4-

- pyridinyloxy)phenyl]sulfonyl] 3thiomorpholinecarboxamide,
  - 12) CollaGenex Pharmaceuticals CMT-3 (Metastat),
    6-demethyl-6-deoxy-4dedimethylaminotetracycline,
- 13) Chiroscience D-2163, 2- [1S- ([(2R,S)-acetylmercapto- 5- phthalimido]pentanoyl- L-leucyl)amino- 3- methylbutyl]imidazole,

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14)

N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

15)

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15

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4 (trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

16)

N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinearboxamide, WO 00/37107

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17)

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4piperidinecarboxamide monohydrochloride,

18)

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4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

19)

4-[[4-(4-

chlorophenoxy)phenyl]sulfonyl]tetrahydro-Nhydroxy-2H-pyran-4-carboxamide,

20)

N-hydroxy-4-[[4-(4-

methoxyphenoxy)phenyl)sulfonyl]-1-(2-

propynyl)-4-piperidinecarboxamide,

21)

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1-cyclopropyl-4-[[4-[(4-

fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-

4-piperidinecarboxamide,

22)

1-cyclopropyl-N-hydroxy-4-[[4-

(phenylthio)phenyl]sulfonyl]-4-

piperidinecarboxamide,

23)

tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide, and

24)

5

tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2Hpyran-4-carboxamide.

# (19) World Intellectual Property Organization International Bureau





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23 December 1998 (23.12.1998) US

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- With international search report.
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

/37107 A

(54) Title: USE OF CYCLOOXYGENASE-2 INHIBITOR, A MATRIX METALLAPROTEINASE INHIBITOR, AN ANTINEO-PLASTIC AGENT AND OPTIONALLY RADIATION AS A COMBINATION TREATMENT OF NEOPLASIA

Inter anal Application No PCT/US 99/30776

CLASSIFICATION OF SUBJECT MATTER A61P35/00 A61K41/00 IPC 7 A61K45/06 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. WO 98 16227 A (GORDON GARY B ; SEARLE & CO Υ 1-145 (US); SEIBERT KAREN (US); MASFERRER JAI) 23 April 1998 (1998-04-23) cited in the application page 3, line 1-8 X 146-149 page 24, line 7 -page 29, line 6 claim 2 WO 97 48685 A (GLAXO GROUP LTD) Υ 1-145 24 December 1997 (1997-12-24) page 10, line 6,7 claims 17-24 Further documents are listed in the continuation of box C. Patent family members are listed in annex. Special categories of cited documents: "T" later document published after the international filing date or priority date and not in conflict with the application but "A" document defining the general state of the art which is not considered to be of particular relevance cited to understand the principle or theory underlying the invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date "L" document which may throw doubts on priority claim(s) or involve an inventive step when the document is taken alone which is cited to establish the publication date of another citation or other special reason (as specified) "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the "O" document referring to an oral disclosure, use, exhibition or document is combined with one or more other such documents, such combination being obvious to a person skilled other means document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report **2** 3. 06. 00 9 June 2000 Name and mailing address of the ISA Authorized office: European Patent Office, P.B. 5818 Patentiaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Herrera, S Fax: (+31-70) 340-3016

Inte onal Application No PCT/US 99/30776

		PC1/US 99/3U//6								
C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT										
Category °	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.							
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P,Y	EP 0 927 555 A (SANKYO CO) 7 July 1999 (1999-07-07) claim 42 page 24, line 28-34		1-145							
P,Y	WO 99 21583 A (WARNER LAMBERT CO ;SUN YI (US)) 6 May 1999 (1999-05-06) claims 1-8		1-145							
X	WO 98 22101 A (RAZ AMIRAM ; MASFERRER JAIME L (US); SEARLE & CO (US)) 28 May 1998 (1998-05-28) page 43, line 5-9 page 3, line 32-34		146-149							
E	EP 0 985 666 A (PFIZER) 15 March 2000 (2000-03-15) page 20, line 25-36		146-149							

Intel lational application No. PCT/US 99/30776

Box I Ob ervations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Claims Nos.:  because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  See FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
see additional sheet
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest  The additional search fees were accompanied by the applicant's protest.  X  No protest accompanied the payment of additional search fees.

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-149 relate to an extremely large number of possible products and/or methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the products and/or methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the general concept, i.e. the triple combination treatment in general.

It is further pointed out that the second invention, i.e. the invention as claimed in claims 146-149 also lacks unity. The only feature being common for the compounds disclosed in claim 146 is that they are all MMP inhibitors.

Both wo

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-145

Use of a COX-2 inhibitor, a MMP inhibitor, an antineoplastic agent selected from a defined group and optionally radiation for the treatment or prevention of a neoplasia disorder and combinations (products) comprising said three active components

2. Claims: 146-149

Use of a COX-2 inhibitor and a MMP inhibitor selected from a defined group for the treatment or prevention of a neoplasia disorder and combinations (products) comprising said active components.

information on patent family members

Inte onal Application No
PCT/US 99/30776

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